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**CRITERES DE JUGEMENT DANS LES ESSAIS CONTROLES RANDOMISES EN
REANIMATION**

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A mon père,

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Résumé Français

Le choix des critères de jugement (principal et secondaires) est une étape essentielle de la construction d'un essai contrôlé randomisé.

Notre premier travail a été de réaliser une revue systématique sur la place des critères de jugement importants pour les patients ou *patient-important outcomes* dans les essais contrôlés randomisés en réanimation. Nous avons défini les *patient-important outcomes* comme étant la mortalité d'une part, et l'impact fonctionnel et sur la qualité de vie des séquelles de la réanimation d'autre part. En effet, en réanimation, les deux objectifs thérapeutiques principaux sont d'une part éviter le décès des patients et d'autre part réduire l'impact des séquelles à moyen et long terme chez les survivants. Nous avons montré que les *patient-important outcomes* ne représentent qu'une proportion faible (27/112, 24%) des critères de jugement principaux des essais publiés en 2013 et que pour une grande majorité il s'agissait d'un critère de mortalité. Une analyse sur les essais publiés au premier semestre 2016 a montré qu'il n'y avait pas eu d'évolution (25% des critères de jugement principaux étaient des *patient-important outcomes*).

Puis, en réalisant une étude ancillaire de cette revue systématique, nous avons investigué l'impact potentiel des décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives quand le critère de jugement était la mortalité, et décrit les données rapportées sur ces limitation(s) ou d'arrêt(s) des thérapeutiques actives dans les essais en réanimation. Nous avons montré que très peu d'essais contrôlés randomisés en réanimation (6/65, 9%) rapportaient le taux de décision de limitation(s) ou d'arrêt(s) des thérapeutiques actives, bien que ces décisions soient fréquentes en pratique clinique. Pour explorer l'impact qu'un déséquilibre de ces décisions entre les 2 bras d'un essai pouvait avoir en termes de biais sur la mortalité, nous avons réalisé une étude de simulation. Cette étude a montré notamment que lorsque ces décisions étaient prises de façon plus tardive dans le groupe expérimental, l'intervention pouvait apparaître protectrice alors même qu'il n'existait pas de réel effet sur la survie.

Enfin, nous avons conduit un essai contrôlé randomisé en réanimation (étude AKIKI, *Artificial Kidney Initiation in Kidney Injury*) en utilisant la mortalité comme critère de jugement principal et en rapportant le taux et le délai des décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives dans les 2 bras.

Résumé Anglais

The choice of relevant primary and secondary endpoints is an essential step of the design of a randomized controlled trial.

In our first work, we conducted a systematic review on patient-important outcomes in randomized controlled trials in critically ill patients. Indeed, clinical decision-making by ICU physicians now pursues the goal of improving mean and long-term outcomes in survivors in addition to increasing their chance of survival. We defined patient-important outcomes as on one hand, outcomes involving mortality at any time, and on the other, quality of life and functional outcomes assessed after ICU discharge. We found that a minority of primary outcomes (27/112, 24%) used in randomized controlled trials published in 2013, were patient-important outcomes and that mortality accounted for the vast majority of them. Our analysis of most recently published trials (first half 2016) showed that patient-important outcomes were used in the same low proportions (25% of the primary outcomes were patient-important outcomes)

We then addressed the question of how well withholding and withdrawal of life support therapies (W-WLST) decisions were reported in RCT in critically ill patients and how such decisions could impact mortality as outcome measure in these trials. We found that W-WLST decisions, although being a daily concern in routine practice, were scarcely reported in these trials, since they appeared in only 6 of 65 (9%) during follow-up. We further explored the impact of an imbalance in such decisions between the 2 arms of a randomized controlled trial, through a simulation study. This simulation showed that the intervention could appear as protective, if the decision of W-WLST was delayed in the interventional arm, even though the intervention had no true effect on survival.

Finally, we performed a randomized controlled study (*Artificial Kidney Initiation in Kidney Injury*, AKIKI) using mortality as primary outcome and paid attention to report the rate of W-WLST decisions in the 2 arms.

Extrait du livre, « *Sepsis and afterwards* », de Idelette Nutma :

“In 2007, I got ill due to a septic shock, and spent 5 days in ICU, related to a Hantavirus infection. My condition was critical and my family was informed that 'it could go either way', leaving them between hope and fear. Fortunately, thank God, I turned the corner, after having been ventilated for a few days. It was not until my discharge that I came to understand the extensive process of recovery after critical illness. Moreover, I came to realize that the need for explanation, support and advice, as well as the importance of providing the patient with a good start of the recovery process, was seriously underestimated. Having been a former nurse, I considered this an important eye opener.

In coping with your sequelae information and tips are so important! During my recovery I felt like I was in ‘No man’s-Land’, and that’s what it feels like for most people. No one *ever* mentioned the word sepsis to them, neither to me. And when I eventually found out, I wanted to know all about it and share it. For that reason I also joined the network called Family and Patient Centered Intensive Care, because the survivors of sepsis and their relatives are often the survivors of ICU as well, and they really need extra attention.”

En France, la recherche clinique est définie par le Code de la santé publique comme « une recherche organisée et pratiquée sur l'être humain en vue du développement des connaissances biologiques ou médicales ». La participation des patients est donc au centre de cette définition.

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Publications liées à la thèse

1/ **Stéphane Gaudry**, Jonathan Messika, Jean-Damien Ricard, Tanissia Boukertouta, Sylvie Guillo, Blandine Pasquet, Emeline Dubief, Didier Dreyfuss, Florence Tubach

Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review

Soumis à Annals of Intensive Care

2/ Jonathan Messika*, **Stéphane Gaudry***, Florence Tubach, Sylvie Guillo, Didier Dreyfuss, David Hajage**, Jean-Damien Ricard**

Withdrawal of life support therapies reporting in randomized controlled trial in critically ill patients: a systematic review and a statistical simulation study

En cours de rédaction

3/ **Stéphane Gaudry**, David Hajage, Frédérique Schortgen, Laurent Martin-Lefevre, Florence Tubach, Bertrand Pons, Eric Boulet, Alexandre Boyer, Nicolas Lerolle, Guillaume Chevrel M.D, Dorothee Carpentier, Alexandre Lautrette M.D., Anne Bretagnol, Julien Mayaux, Marina Thirion, Philippe Markowicz, Guillemette Thomas, Jean Dellamonica, Jack Richecoeur, Michael Darmon, Nicolas de Prost, Hodane Yonis, Bruno Megarbane, Yann Loubières, Clarisse Blayau, Julien Maize, Benjamin Zuber, Saad Nseir, Naïke Bigé, Isabelle Hoffmann, Jean-Damien Ricard, Didier Dreyfuss

Comparison of 2 strategies for initiating renal replacement therapy in the intensive care unit: study protocol for a randomized controlled trial (AKIKI)

Publié dans Trials (2015;16:170)

4/ **Stéphane Gaudry**, David Hajage, Frédérique Schortgen, Laurent Martin-Lefevre, Bertrand Pons, Eric Boulet, Alexandre Boyer, Guillaume Chevrel, Nicolas Lerolle, Dorothee Carpentier, Nicolas de Prost, Alexandre Lautrette, Anne Bretagnol, Julien Mayaux, Saad Nseir, Bruno Megarbane, Marina Thirion, Jean-Marie Forel, Julien Maizel, Hodane Yonis, Philippe Markowicz, Guillaume Thiery, Florence Tubach, Jean-Damien Ricard, Didier Dreyfuss, for the AKIKI study group

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

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1/ INTRODUCTION

1-1 Le contexte de la réanimation

Depuis la création des premiers services de réanimation dans les années 50 à l'occasion de la pandémie de poliomyélite et de la prise en charge de l'insuffisance rénale aiguë, la médecine de soins intensifs s'est fortement développée grâce notamment à la compréhension des mécanismes physiopathologiques des maladies prises en charge et aux progrès technologiques (ventilation mécanique, épuration extra-rénale, monitoring invasif,...) (1). Le nombre de patients hospitalisés en réanimation (près de 5 millions chaque année en Europe) augmente parallèlement à l'âge et à la fréquence des comorbidités de la population (2). Dans ce domaine, les publications scientifiques majeures étaient jusqu'aux années 90 essentiellement des études observationnelles physiologiques (3, 4). L'avènement de la médecine basée sur les preuves (« *evidence-based medicine* ») (5) a modifié en profondeur les caractéristiques des publications dans ce domaine et rendu l'essai contrôlé randomisé la pierre angulaire de la recherche clinique en réanimation. Ainsi, le nombre d'essais contrôlés randomisés publiés en réanimation a considérablement augmenté au cours des 2 dernières décennies (6–9).

1-1-a L'objectif des soins intensifs

L'objectif premier du développement des unités de soins intensifs était de sauver la vie des patients en situation critique. Cet objectif a été en grande partie atteint dans les principales situations cliniques telles que le choc septique et l'insuffisance respiratoire aiguë du fait des progrès majeurs en terme de prise en charge symptomatique et de traitements étiologiques (6, 10). Bien que cet objectif reste une priorité dans la prise en charge quotidienne des patients hospitalisés dans les services de soins intensifs, d'autres priorités ont récemment émergé. En particulier, après leur séjour en réanimation, de très nombreux patients souffrent de symptômes physiques, mentaux et cognitifs (11) qui peuvent notablement altérer leur qualité de vie. Ainsi, la

prévention de ces séquelles est progressivement apparue comme un nouvel objectif à atteindre dans la prise en charge quotidienne des patients de réanimation.

1-1-b Conséquences de l'hospitalisation en réanimation

Complications physiques

Les patients en situation critique sont sujets à de nombreuses « agressions » au cours de leur séjour en soins intensifs. Les carences nutritionnelles, l'immobilisation et l'hypercatabolisme associé au sepsis sont des exemples d'agressions qui conduisent à des complications musculaires et neurologiques ainsi qu'à une faiblesse générale qui marquent, parfois pendant de nombreux mois, les suites d'un séjour en soins intensifs.

Les polyneuropathies et les myopathies acquises en réanimation touchent près de 50% des patients dans les suites d'un sepsis, d'une défaillance multi-organe ou d'une ventilation mécanique prolongée. De plus, près de 90% des patients ayant présenté une polyneuropathie acquise en réanimation ont encore des anomalies neuromusculaires 5 ans après leur séjour en réanimation (12, 13). L'autonomie de ces patients est limitée par les séquelles physiques du séjour en réanimation. En particulier, les patients ayant nécessité plus de 48 heures de ventilation mécanique (situation extrêmement fréquente) ont, pour près de 70% d'entre eux, une limitation de leurs activités quotidiennes, et moins de la moitié ont repris leur travail après 12 mois de suivi (14, 15).

Ces complications physiques à distance du séjour en réanimation ont été récemment mises en lumière dans un article intitulé : « *Winning the war against ICU-weakness : new innovation in nutrition and exercise physiology* » de Paul Wischmeyer (16). L'auteur de cet article s'appuie notamment sur sa propre expérience de la réanimation en publiant sa photo avant son séjour en réanimation (en tant que patient) puis après (Photographie 1). Cette photographie publiée en 2015 dans la revue

Critical Care (16) montre à quel point un séjour en réanimation, y compris chez un sujet jeune et en bon état général peut avoir des conséquences majeures sur son état physique. Il est ainsi aisé d'imaginer les conséquences physiques d'un séjour en réanimation chez des patients plus âgés souffrant déjà de pathologies chroniques (insuffisance cardiaque, insuffisance respiratoire chronique, etc.).

Photographie 1



Source: Wischmeyer PE, San-Millan I. Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. *Crit Care Lond Engl* 2015;19 Suppl 3:S6 (16)

Complications psychiques

En plus des séquelles physiques, les complications psychiques sont particulièrement fréquentes. En effet, entre 25 et 30% de ces patients souffrent d'une symptomatologie dépressive dans les suites de leur hospitalisation en soins intensifs (17, 18). Le syndrome de stress post-traumatique, initialement décrit chez des soldats au retour de zones de conflits et chez les victimes de catastrophes, est désormais reconnu comme une complication de l'hospitalisation en réanimation (19, 20). Les douleurs (malgré les progrès de l'analgésie), le manque de sommeil ou sa désorganisation (21), l'anxiété liée à la peur de la mort participent à la genèse de ce syndrome.

Dans un article récent (22), le syndrome de stress post-traumatique touchait 27% de patients dans l'année suivant la sortie de réanimation sans différence de proportion entre les patients médicaux, chirurgicaux ou polytraumatisés. L'altération des fonctions cognitives est également décrite dans ces situations et peut persister plusieurs années après la sortie de réanimation (23).

Conséquences générales

Comme nous l'avons précisé précédemment, ces complications physiques et psychiques viennent s'ajouter aux complications spécifiques de maladies sous-jacentes (insuffisance cardiaque, insuffisance respiratoire chronique, diabète, immunodépression, etc.). Néanmoins, il est désormais reconnu que certaines de ces complications telles que la polyneuropathie acquise en réanimation et le syndrome de stress post-traumatique sont indépendantes des antécédents du patient et sont liées directement à la prise en charge en réanimation. Ainsi, la spécificité de ces multiples symptômes a récemment conduit à définir le nouveau terme de « syndrome post-réanimation » (*Postintensive care syndrome*, PICS) (24, 25). Ce terme est désormais recommandé pour décrire une détérioration physique, mentale ou cognitive persistante dans les suites d'une hospitalisation en réanimation.

Les séquelles tant physiques que psychiques des patients victimes d'un syndrome post-réanimation peuvent altérer leur qualité de vie. Depuis quelques années, l'intérêt porté à la qualité de vie après la réanimation a nettement crû au point d'être maintenant considérée comme une priorité de recherche clinique (26). Cependant, les études portant sur la qualité de vie des patients à la sortie de réanimation sont peu nombreuses et sont majoritairement des études de cohorte s'intéressant à la qualité de vie des patients ayant eu une pathologie particulière (syndrome de détresse respiratoire aiguë (SDRA), choc septique,..) (27, 28) après la sortie de réanimation. Elles portent donc sur des situations spécifiques, non sur le syndrome post réanimation d'une manière générale, et ne portent pas sur l'évaluation de thérapeutiques. Ces études montrent qu'un séjour

en réanimation altère la qualité de vie des patients parfois au-delà de 12 mois.

1-2 L'essai contrôlé randomisé, le gold standard de l'évaluation thérapeutique

Un des premiers essais contrôlés randomisés fut publié en 1948 dans le *British Medical Journal* (29). Par la suite, de nombreux développements méthodologiques ont permis de faire des essais randomisés le gold standard de l'évaluation thérapeutique. Ils permettent, grâce à une démarche expérimentale rigoureuse, d'évaluer l'efficacité d'une intervention en santé. Cette intervention peut revêtir des formes différentes : traitement médicamenteux, techniques chirurgicales ou médicales, stratégies plus ou moins complexes de prise en charge, méthodes diagnostiques, ou encore mesures de prévention ou d'éducation en santé.

Le respect d'une rigueur méthodologique à chaque étape de la recherche (choix des critères d'inclusion et de non-inclusion, des critères de jugement, randomisation, standardisation de l'intervention, aveugle etc.) est le gage de la qualité de ces essais.

Un des points clé lors de la conception d'un essai contrôlé randomisé est le choix du critère sur lequel sera jugée l'efficacité de l'intervention. Ce critère est appelé critère de jugement. L'intérêt du résultat d'un essai contrôlé randomisé est en grande partie évalué sur la pertinence de la mesure c'est à dire sur la pertinence du critère de jugement choisi en fonction l'objectif thérapeutique.

Les essais contrôlés randomisés étant les études à plus haut niveau de preuve lorsqu'il s'agit de juger de l'efficacité d'une intervention (30), les recommandations internationales pour la prise en charge des patients s'appuient en grande partie sur les résultats de ces essais (31).

1-3 Problématiques liées aux essais randomisés en réanimation

La spécificité du contexte de la réanimation devrait influencer le choix des critères de jugement utilisés dans les essais en réanimation. En particulier, le taux de décès à court terme de ces patients est important, ce qui soulève les deux problématiques suivantes :

1. La mortalité est assurément un critère cliniquement pertinent dans ce contexte. Néanmoins, depuis plusieurs années, l'amélioration de la survie des patients hospitalisés en réanimation a rendu plus difficile la mise en évidence de l'effet d'une intervention en utilisant la mortalité comme critère de jugement. Ceci a participé à l'abondance d'essais négatifs dans ce domaine (32–36). Par ailleurs, les décisions prises dans le cadre des soins en réanimation ont pour but de limiter la mortalité et d'améliorer la survie dans des conditions les plus acceptables de qualité de vie. Ainsi, les critères de jugement utilisés en réanimation devraient permettre d'éclairer les médecins réanimateurs sur l'impact de l'intervention évaluée en termes de mortalité et de qualité de vie ou de performance fonctionnelle à distance de la sortie de réanimation.
2. Les décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives sont particulièrement fréquentes en réanimation. Ces décisions peuvent conduire accélérer l'occurrence du décès. Par conséquent, de telles décisions peuvent influencer les résultats d'un essai ayant la mortalité en critère de jugement.

Ce sont ces deux problématiques que nous aborderons dans cette thèse.

1-4 Critères de jugement dans les essais contrôlés randomisés

1-4-a Généralités

Les critères de jugement sont des variables dont la valeur numérique est susceptible de se modifier sous l'effet de l'intervention, permettant ainsi la mise en évidence « quantitative » de l'effet de l'intervention. Ces critères peuvent être de nature très variée comme par exemple la durée d'hospitalisation, la survenue d'un événement (embolie pulmonaire, infarctus du myocarde, décès, etc.) ou les coûts.

Le choix du critère de jugement principal lors de la construction d'un essai contrôlé randomisé est donc une étape essentielle. La pertinence des critères de jugement (principal et secondaires) est fondamentale pour interpréter l'effet de l'intervention étudiée. Les résultats portant sur des critères de jugement biologiques ou physiologiques peuvent contribuer à mieux comprendre de quelle façon une intervention peut affecter la santé. Néanmoins ce type de critère de jugement (biologique ou physiologique) ne permet pas d'apprécier dans quelle proportion l'intervention est réellement utile pour le patient.

La pertinence d'un critère de jugement peut se juger sur l'impact clinique pour le patient. Par exemple, un traitement anti-hypertenseur peut être évalué sur sa capacité à contrôler le niveau de la pression artérielle. Ce niveau de pression artérielle n'est pas pertinent pour le patient, qui ne le perçoit pas. A l'inverse, la survenue éventuelle d'un accident vasculaire cérébral 5 ans après, qui peut être la conséquence de l'hypertension artérielle, a une réelle pertinence clinique pour le patient. Un exemple similaire est le traitement de l'hypercholestérolémie qui peut se juger sur la baisse du taux de cholestérol plasmatique ou sur des critères plus pertinents cliniquement comme la survenue d'un infarctus du myocarde.

Parmi les critères de jugement pertinents cliniquement, les critères de jugement rapportés par les patients (ou « *patient-reported outcomes* ») ont émergé il y a plus de 25 ans. Ce sont des mesures de tout aspect de la santé d'un patient qui sont rapportées par le patient lui-même et donc qui ne passent

pas par l'interprétation du médecin ou de l'investigateur. Les *patient-reported outcomes* procurent ainsi une information optimale sur la perception qu'a le patient de l'impact de la maladie sur son quotidien et son bien être, son besoin de prise en charge, ses préférences et priorités quant à son traitement et l'évaluation de son efficacité, le bénéfice qu'il a tiré de son traitement, et ses inconvénients (37).

Plus récemment, certains auteurs ont mis en lumière les limites des critères de jugement dits « pertinents cliniquement » et ont suggéré des termes alternatifs plus explicites tels que « *patient-oriented outcomes* » (38) ou « *personal significance* » (39). En effet, la variation de la fraction d'éjection du ventricule gauche ou de la capacité pulmonaire totale peuvent être des critères pertinents cliniquement du point de vue du médecin, mais ne pas avoir d'importance lorsque l'on se place dans la perspective du patient et que l'on intègre son vécu et son ressenti. Finalement, le terme de *patient-important outcomes* (critères de jugement importants pour les patients, que nous nommerons au cours de ce manuscrit par leur terme anglo-saxon) a été choisi et repris dans de nombreux articles car il reflète la perception et l'interprétation individuelles de la pertinence d'un critère de jugement (40). Les *patient-important outcomes* ont ensuite été promus dans différents domaines tel que la rhumatologie et la diabétologie (41, 42). Leur place dans la recherche en soins intensifs et réanimation n'a cependant jamais été évaluée.

1-4-b Classifications des critères de jugement

Afin de mieux comprendre les propriétés et les relations des critères de jugement utilisés dans les essais cliniques, plusieurs classifications ont été proposées.

Dans un premier temps, les critères de jugement ont été classés en fonction du type de données recueillies. Il peut s'agir de données biologiques (exemple : le taux de créatinine plasmatique, le taux de cholestérol), cliniques (exemple : l'embolie pulmonaire, l'infarctus du myocarde), de

survie (la mortalité pouvant être évaluée à différents moments) ou de structure (exemple : épaisseur d'un tissu, réponse tumorale radiologique).

Par la suite, la source de la donnée recueillie a permis de proposer une autre classification. On distingue classiquement les critères de jugement dont la source est le patient ou *patient-reported outcomes* (douleur, fonction, qualité de vie), ceux dont la source est le médecin ou *physician-driven data* (examen clinique), les examens complémentaires (biologie, radiologie) et les événements cliniques (infarctus du myocarde, embolie pulmonaire). On peut également individualiser les critères de jugement rapportés par les aidants ou l'entourage qui ont des caractéristiques similaires à ceux rapportés par les patients (*patient-reported outcomes*).

Enfin, on peut les classer en fonction de leur degré d'objectivité. Le résultat d'un dosage sanguin ou le décès sont des données objectives alors que l'évaluation de la douleur ou de la qualité de vie sont beaucoup plus subjectives.

1-4-c Taxonomie des critères de jugement

Afin de mieux décrire les relations qui existent entre les différents critères de jugement, plusieurs modèles ont été proposés.

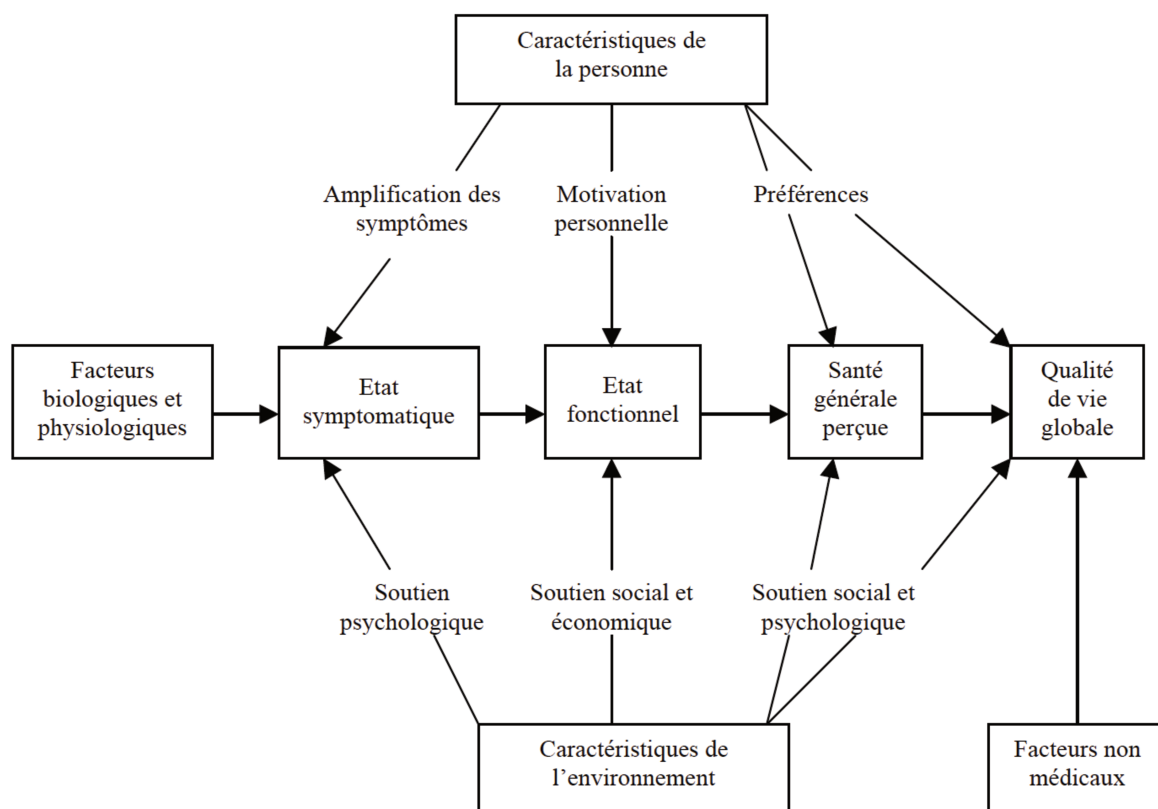
Modèle de Wilson et Cleary

Ce modèle proposé en 1995 classe les critères de jugements en 5 catégories (43) :

- Les mesures biologiques et physiologiques : mesures objectives correspondant à l'évaluation de la fonction d'une cellule, d'un organe ou d'un tissu.
- Les symptômes : perception subjective des patients de leur état physique ou psychique.

- Le fonctionnement : évaluation de la capacité à réaliser des tâches ou fonctions spécifiques (physiques, sociales ou émotionnelles).
- La santé générale perçue : perception globale du patient de sa santé incluant une échelle de valeur qu'il accorde aux différents symptômes ou incapacité fonctionnelle.
- La qualité de vie globale : mesure de satisfaction globale par rapport à sa propre vie qui peut être sans lien avec la santé.

Figure 1 : Relation dynamique entre 5 types de critères de jugement selon le modèle de Wilson et Cleary (43)



Source : Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.

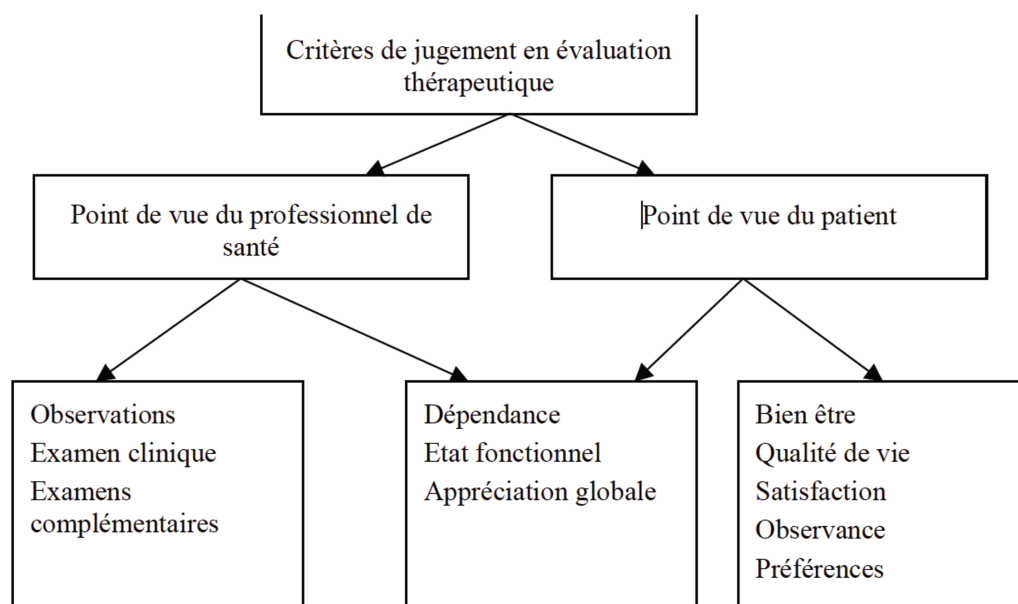
Ce modèle décrit la relation dynamique entre les 5 types de critères de jugement, ainsi que l'impact sur ces critères des caractéristiques propres à la personne et de son environnement. Dans ce modèle :

- chaque type de critère de jugement a un impact potentiel sur celui situé à sa droite
- de gauche à droite, les critères de jugement correspondent à des critères de plus en plus complexes et intégrés, et l'influence des caractéristiques propres à la personne et de son environnement sont de plus en plus importante (Figure 1).

Modèles introduisant les *patient-reported outcomes*

Le modèle de Patrick et Chiang (Figure 2a) proposé en 2000 a pour particularité de s'intéresser à la source c'est à dire à l'individu qui rapporte le critère (le professionnel de santé ou le patient) (44). Il introduit donc le concept de critère de jugement rapporté par le patient ou *patient-reported outcome*.

Figure 2a : Modèle de Patrick et Chiang (44)



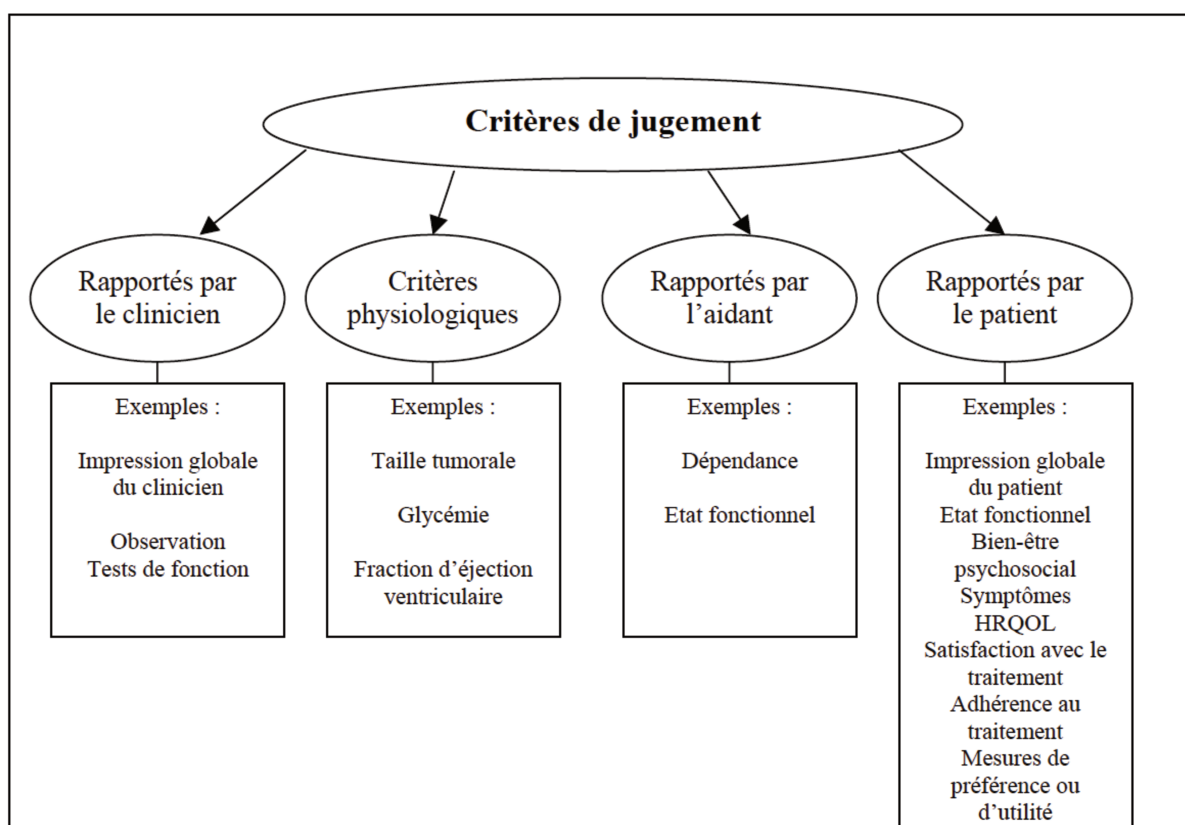
Source: Patrick DL, Chiang YP. Measurement of health outcomes in treatment effectiveness

evaluations : conceptual and methodological challenges. Med Care 2000 ;38 (Suppl) : II14 –II25.

La définition des *patient-reported outcomes* recouvre de nombreux critères de jugement tels que la fréquence et la sévérité des symptômes (douleur, dyspnée, fonction...), la qualité de vie liée à la santé, l'adhérence au traitement et la satisfaction des soins reçus (45).

Dans un modèle un peu plus complet proposé par la FDA (*Food and Drug Administration*) en 2001, la notion de critère de jugement rapporté par l'aidant a été introduit et a permis d'harmoniser les pratiques en proposant que le terme général de *patient-reported outcome* soit utilisé pour tous les critères de jugement rapportés subjectivement par les patients ou leurs proches (46) (Figure 2b).

Figure 2b : Modèle du PRO Harmonization Group



Source: Acquadro C, Berzon R, Dubois D, Leidy NK, Marquis P, Revicki D, Rothman M, PRO Harmonization Group. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO)

1-4-d Les critères de jugement intermédiaires

Les critères de jugement intermédiaires (*surrogate endpoints*) ne mesurent pas directement un objectif thérapeutique cliniquement pertinent mais ils mesurent des variables souvent physiologiques susceptibles de se modifier sous l'effet du traitement étudié, et sur lesquelles l'impact du traitement va dans le même sens que l'impact sur le critère de jugement cliniquement pertinent (ils se trouvent sur le chemin causal entre l'exposition au traitement et la survenue ou non de l'évènement cliniquement pertinent). Ils ont pour intérêt de se modifier plus tôt que la variable d'intérêt clinique, et sont généralement des variables continues, ce qui permet de montrer une différence entre les deux bras d'un essai avec un effectif moindre que pour la variable d'intérêt clinique, généralement binaire et de fréquence parfois rare (ex : cholestérolémie à 3 mois *vs* infarctus du myocarde à 5 ans). Le tableau 1 décrit des exemples de critères de jugement intermédiaires en rapport avec des critères de jugement cliniques dans différentes pathologies.

Tableau 1 : Relation entre pathologie, critère de jugement intermédiaire et critère de jugement clinique

Pathologie	Critère de jugement intermédiaire	Critère de jugement clinique
Hypertension	Pression artérielle	Événements coronariens, AVC
Ostéoporose	Densité osseuse	Fracture du col du fémur
Rhumatisme inflammatoire	Vitesse de sédimentation	Handicap fonctionnel
Diabète	Hémoglobine glycosylée	Rétinopathie, évènements cardiovasculaires, insuffisance rénale

Les enjeux liés à l'évaluation des carrières et des structures de recherche qui se base sur la quantité de publications et leur impact factor poussent les chercheurs et les laboratoires à obtenir

des résultats rapidement. Ceci favorise l'utilisation de ces critères de jugement intermédiaires. La littérature donne de nombreux exemples des risques liés à l'utilisation de ce type de critères de jugement. Par exemple, la prescription de flecaïne après un épisode d'infarctus du myocarde a démontré son efficacité en terme de réduction des arythmies cardiaques (ce qui apparaît à première vue comme un bénéfice) mais est associée à une augmentation de la mortalité à moyen et long terme, ce qui est assurément le critère de jugement cliniquement pertinent (47). De la même façon, l'hormone de croissance a montré qu'elle améliorait la balance azotée des patients mais qu'elle augmentait la mortalité en réanimation (48).

1-4-e Les critères de jugement importants pour les patients ou *patient-important outcomes*

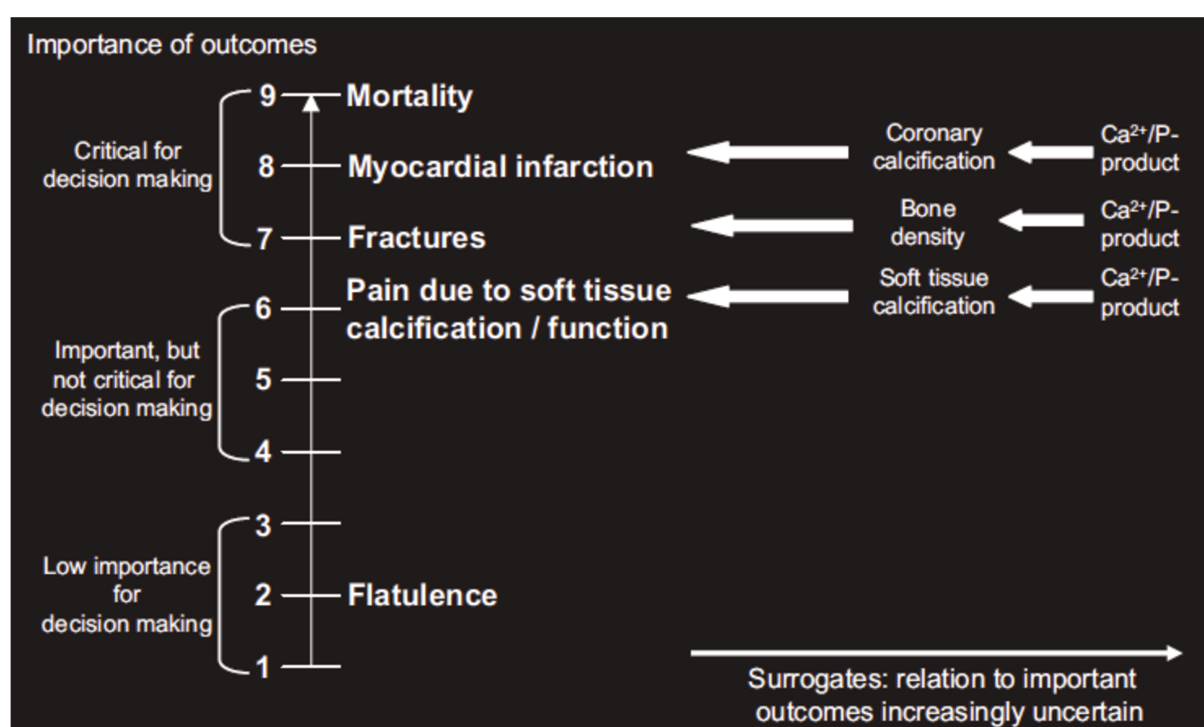
Naissance et développement des *patient-important outcomes*

Le terme de *patient-important outcomes* est apparu au début des années 2000. Dans l'article « *Patients at the center : In our practice and in our use of language* », Gordon Guyatt décrit comment l'évolution des mentalités des cliniciens a conduit à la naissance de ce nouveau terme (40).

En pratique clinique, le rapport médecin-patient a longtemps suivi un modèle paternaliste dans lequel le patient n'est pas doué de raison et n'est capable ni de comprendre sa maladie ni de décider pour lui-même. Ce modèle a longtemps influencé la recherche clinique et abouti à exclure les patients du processus de recherche, le cantonnant au rôle de sujet de la recherche. Il a connu une évolution progressive vers un modèle plus autonomiste laissant une part conséquente aux préférences du patient dans le choix des thérapeutiques. La décision médicale est maintenant une décision partagée entre le médecin et le patient qui nécessite cependant une information médicale compréhensible et loyale permettant d'éclairer les choix du patient. Pour éclairer ces choix, il est important de disposer de données de qualité portant sur l'effet des interventions sur des critères importants pour les patients.

Des classifications de critères de jugement en fonction de leur importance vis à vis de la décision médicale ou en fonction de leur rapport plus ou moins fort avec une autre variable importante pour la décision médicale ont été proposées (49). Les auteurs de cette classification soulignent que l'importance de ces critères varie en fonction de la perspective dans laquelle on se place (celle du patient ou celle du clinicien). La Figure 3 montre un exemple de cette hiérarchisation avec l'exemple des critères de jugement utilisés pour l'évaluation des traitements de l'hyperphosphorémie chez l'insuffisant rénal chronique.

Figure 3 : Importance des critères de jugement utilisés dans l'évaluation des traitements de l'hyperphosphorémie chez l'insuffisant rénale chronique



Source : Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2011;64:395–400.

En recherche clinique les *patient-important outcomes* ont été définis comme une caractéristique ou variable reflétant ce que le patient ressent, comment il fonctionne ou comment il survit (50, 51). Ce sont donc des critères de jugement qui prennent en considération les valeurs et les préférences

des patients. De ce fait, leurs caractéristiques sont pour partie culturelles au sens sociologique du terme. Les *patient-important outcomes* peuvent donc revêtir des notions différentes d'une population à une autre. Il est néanmoins admis que, quelle que soit la population, la mortalité et la qualité de vie font partie des *patient important outcomes* (42).

Les *patient-important outcomes* se distinguent des *patient-reported outcomes* car ils ne sont pas nécessairement rapportés par le patient. La mortalité est un bon exemple de *patient-important outcomes* dont la source n'est pas directement le patient. Les *patient-important outcomes* englobent néanmoins une grande partie des *patient-reported outcomes*.

Dans le domaine des maladies rhumatologiques, il a été montré que les patients percevaient la réalité de leur état de santé et l'impact qu'il a sur leur vie de façon plus précise que leur médecin (52). Ceci soutient l'importance de prendre en considération la perspective du patient dans l'évaluation des thérapeutiques et souligne donc le lien étroit entre *patient-reported outcomes* et *patient-important outcomes*.

James Lind Alliance au Royaume Uni (53, 54) et le *Patient Centered Outcome Research Institute* aux Etats Unis (55–58) ont souligné la non concordance qui existe souvent entre d'une part les questions que les patients se posent et d'autre part les questions abordées par les chercheurs. Cette situation a conduit certains leaders d'opinion en recherche biomédicale à appeler à une « révolution des patients » (59). Dans l'article intitulé : « *Let the patient revolution begin* », les auteurs insistent sur l'importance du développement d'un véritable partenariat entre patients, soignants et chercheurs afin d'améliorer le système de soin en prenant en compte les préférences et les attentes des patients (59).

Les données sur la place des *patient-important outcomes* dans la recherche biomédicale sont encore peu nombreuses. En 2003, l'équipe de Victor Montori a publié une revue systématique sur la qualité des essais cliniques randomisés dans le domaine du diabète (60). Dans ce travail, seuls 21% des essais rapportaient un *patient-important outcome* comme critère de jugement principal. En

2008, dans une autre étude s'intéressant à des essais cliniques en cours et référencés dans des registres d'essais (donc plus récents que les essais déjà publiés), la même équipe montrait que seuls 18% des essais en diabétologie utilisaient un *patient-important outcome* comme critère de jugement principal et donc qu'il ne semblait pas y avoir d'amélioration récente (42).

Patient-important outcomes et réanimation

Les décisions thérapeutiques des réanimateurs sont guidées par deux objectifs principaux : d'une part éviter le décès des patients et d'autre part réduire l'impact des séquelles à moyen et long terme chez les survivants, en particulier en termes d'état fonctionnel, de santé générale perçue et de qualité de vie. En considérant la perspective du patient, il semble légitime que l'effet d'une intervention soit évalué sur un critère de jugement en rapport avec ces priorités.

De nombreux critères de jugement utilisés en réanimation sont évalués à court terme (61). Leur impact sur les conséquences à long terme n'a pas été clairement évalué. On sait néanmoins que certaines dysfonctions aiguës d'organe en réanimation n'ont pas de conséquence significative sur des critères de jugement à long terme centrés sur le patient. Dans une large étude observationnelle menée dans les années 90, l'apparition d'une défaillance aiguë d'organe au cours du séjour en réanimation n'était pas associée à une augmentation de la mortalité à trois mois ni à une altération de la qualité de vie après ajustement sur l'état de base précédant l'hospitalisation en réanimation (62).

Bien que la qualité de vie après la sortie de réanimation soit à l'évidence un *patient-important outcome*, elle n'est que rarement étudiée dans les essais randomisés en réanimation. Cette carence n'est pas le reflet d'un manque d'intérêt des réanimateurs pour cette problématique mais possiblement le reflet de leur pratique où ils ne revoient que rarement les patients après leur sortie. De nombreuses décisions thérapeutiques sont néanmoins prises par les réanimateurs après une réflexion sur l'impact de celles-ci sur la qualité de vie future (supposée) du patient (63).

La place des *patient-important outcomes* dans les essais en réanimation n'a jamais été évaluée. Compte tenu des spécificités des patients hospitalisés en soins intensifs (cf Chapitre : Conséquences de l'hospitalisation en réanimation), il serait pertinent qu'ils soient largement évalués.

En se référant à la définition générale des *patient-important outcomes* (50, 51) et en considérant les spécificités de la réanimation, nous avons donc considéré que dans le domaine de la recherche en soins intensifs, les *patients-important outcomes* recouvraient deux types de critères de jugement :

1. la mortalité (quel que soit le délai de son évaluation)
2. les critères de jugement rapportés par les patients évalués après le séjour en réanimation, comprenant la qualité de vie, la santé perçue et les capacités fonctionnelles

1-5 Limitation(s) et arrêt(s) des thérapeutiques actives

1-5-a Définitions et place en réanimation

Les décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives prises ont pour objectif de préserver la dignité du patient en fin de vie.

D'après les Recommandations de la Société de Réanimation de Langue Française de 2002 :

Les limitations des thérapeutiques actives sont définies par la non-instauraton ou la non-optimisation d'une ou plusieurs thérapeutique(s) curative(s) ou de suppléance des défaillances d'organes, dont la conséquence peut être d'avancer le moment de la mort.

L'arrêt des thérapeutiques actives est défini par l'arrêt d'une ou plusieurs thérapeutique(s) curative(s) ou de suppléance des défaillances d'organes déjà instituée(s), dont la conséquence peut être d'avancer le moment de la mort.

Les décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives peuvent concerner un très grand nombre de thérapeutiques utilisées en réanimation en particulier les supports de défaillance d'organe (catécholamines, ventilation mécanique, épuration extra-rénale, etc.). Du fait de l'amélioration des performances de ces supports d'organes, ces décisions sont de plus en plus indispensables afin d'éviter les situations d'acharnement thérapeutique contraires au code de déontologie médicale et à la loi qui a préféré les qualifier « d'obstination déraisonnable ». Elles sont d'ailleurs très encadrées par la législation.

De telles décisions sont prises chez près de 10% des patients admis en réanimation (64–66). De plus, au moins 50% des patients qui décèdent en réanimation ont fait l'objet d'une limitation ou d'un arrêt de traitement (66). Comme le précise la définition de ces limitation(s) ou arrêt(s) des thérapeutiques actives, le moment de ces décisions peut avoir pour conséquence d'avancer le moment de la mort.

1-5-b Implication pour les essais contrôlés randomisés en réanimation

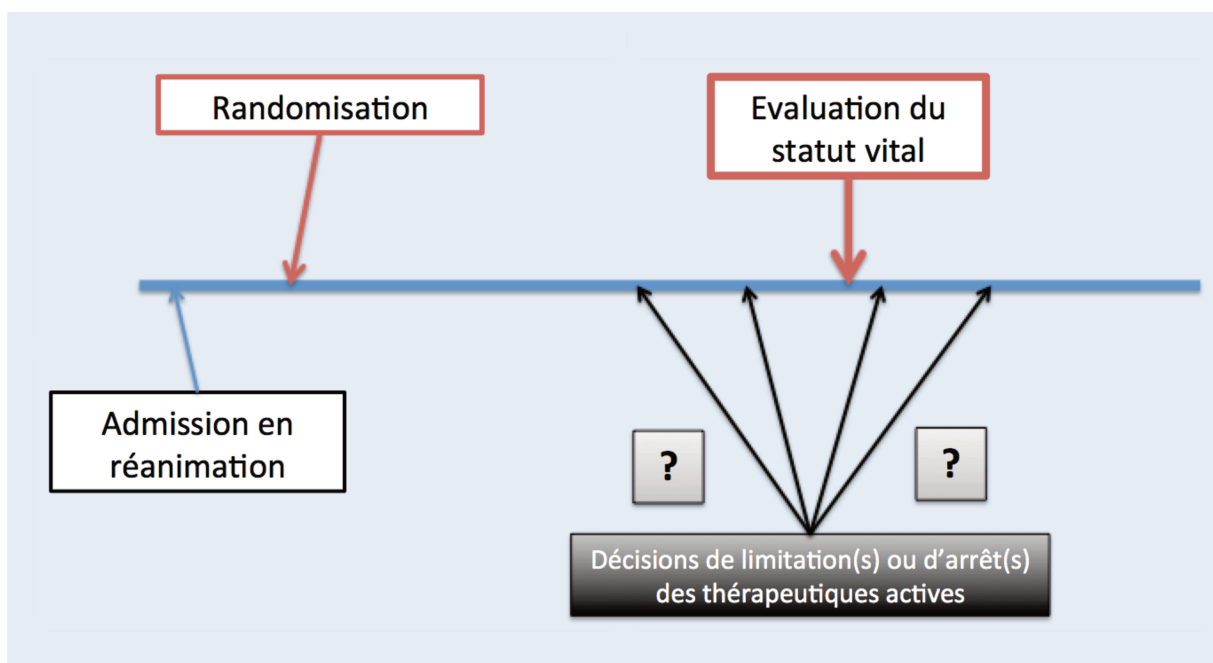
Les décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives ne sont pas systématiquement suivies du décès du patient. Néanmoins, chez un nombre important de patients, ces décisions accélèrent l'occurrence du décès en particulier lors de l'arrêt de la ventilation mécanique invasive. Par conséquent, lorsqu'un essai thérapeutique utilise la survie comme critère de jugement principal, on peut faire l'hypothèse que le délai entre la randomisation et la décision de limitation(s) ou d'arrêt(s) des thérapeutiques actives ainsi que le *timing* de cette décision par rapport à la fin du suivi prévu (temps de recueil du statut vital) peuvent influencer le délai de l'occurrence de l'événement « décès » pendant le suivi du patient dans l'essai.

Ainsi, un déséquilibre dans ces prises de décisions (sur leur fréquence et/ou sur leur délai par rapport à la randomisation) entre les 2 bras d'un essai contrôlé randomisé pourrait avoir comme conséquence de créer une différence de survie entre les 2 groupes (Figure 4).

Cette différence pourrait alors s'expliquer de 2 façons :

- une différence d'efficacité réelle entre les 2 interventions comparées dans l'essai, par l'intermédiaire de leur effet sur les prises de décision
- et/ou un biais de performance (particulièrement plausible dans des essais en ouvert qui sont très fréquents en réanimation).

Figure 4 : Influence du moment de la prise de décision de limitation(s) ou d'arrêt(s) des thérapeutiques sur l'interprétation d'un critère de jugement de survie en réanimation.



Le biais de performance peut donc avoir une conséquence non négligeable sur la mortalité à un temps donné (exemple: mortalité à J28).

Pour limiter le biais de performance qui peut donc avoir une conséquence non négligeable sur le critère de jugement, il apparaît nécessaire que ces décisions de limitation(s) ou d'arrêt(s) des

thérapeutiques actives soient si possible prises de manière standardisée, sur la base de critères consensuels, et rapportées de façon précise dans les différents bras des essais contrôlés randomisés en réanimation, notamment lorsque l'essai utilise la mortalité comme critère de jugement et que l'essai est en ouvert.

Il serait utile, lors de la présentation des résultats d'un essai, de disposer des informations suivantes : nombre et délai des décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives dans chaque bras jusqu'à la date du recueil du critère de jugement et sur une période définie après la date de ce recueil. En effet, une augmentation du nombre de ces décisions dans le bras expérimental après cette date pourrait permettre la mise en évidence et la quantification de ce biais potentiel.

1-6 Objectifs de la thèse

Les objectifs de ce travail étaient les suivants :

- Définir et évaluer la place des *patient-important outcomes* dans les essais contrôlés randomisés en réanimation.
- Décrire si les décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives étaient correctement rapportées dans les essais contrôlés randomisés en réanimation et évaluer leur impact potentiel sur les résultats en termes de mortalité.
- Mettre en application les recommandations issues de ces deux travaux dans le cadre d'un essai contrôlé randomisé en réanimation utilisant un *patient-important outcome* comme critère de jugement principal et rapportant le taux de décisions de limitations thérapeutiques dans les 2 bras de l'essai.

Pour répondre à ces objectifs, notre travail de recherche s'est articulé autour de la réalisation d'une revue systématique de la littérature et de la réalisation d'un essai clinique en réanimation.

2/ PLACE DES *PATIENT-IMPORTANT OUTCOMES* DANS LES ESSAIS CONTROLES RANDOMISES EN REANIMATION

2-1 Objectif

Notre objectif était d'évaluer la place des *patient-important outcomes* dans les essais contrôlés randomisés en réanimation.

2-2 Méthodologie

Nous avons réalisé une revue systématique des essais contrôlés randomisés en réanimation publiés en 2013. L'extraction des données (données générales, méthodes, qualité, caractéristiques des études, caractéristiques des patients) s'est faite grâce à deux lectures indépendantes (Jonathan Messika et Stéphane Gaudry) de l'ensemble des articles.

Une étape clé de ce travail fut le développement d'une classification de l'ensemble des critères de jugement adaptée au contexte des essais en réanimation. Cette classification comprend 6 catégories :

1. *Patient-important outcomes* qui recouvraient 2 entités comme décrit plus haut : la mortalité d'une part et d'autre part les critères de jugement rapportés par les patients évalués après le séjour en réanimation, comprenant la qualité de vie, la santé perçue et les capacités fonctionnelles.
2. Critères de jugement cliniques au cours de l'hospitalisation tels que : défaillances d'organe, complications et effets secondaires des thérapeutiques, infections nosocomiales, delirium, autres évènements cliniques (embolie pulmonaire, souffrance myocardique), douleur, anxiété, niveau de conscience, sommeil, réponse aux antibiotiques, dyspnée.

3. Critères de jugement biologiques/physiologiques/radiologiques tels que les dosages de Brain Natriuretic Peptide (BNP) ou de Neutrophil Gelatinase Associated Lipocalin (NGAL), la capacité pulmonaire ou les scores radiologiques.
4. Critères de jugement en rapport avec une décision médicale tels que les durées de ventilation mécanique, d'hospitalisation, d'exposition aux antibiotiques, le recours à l'intubation, la trachéotomie, la transfusion, la sédation ou d'autres thérapeutiques médicamenteuses.
5. Critères de jugement en rapport avec la performance des soins tels que la qualité d'une procédure (exemple : la durée pour réaliser une intubation), l'exposition au bruit et à la lumière.
6. Les autres critères : la satisfaction des familles ou des soignants, les coûts, les limitations thérapeutiques, la charge de travail, la compliance à un protocole ou les conflits médico-légaux.

Afin de vérifier que la distribution des types de critères de jugement ne s'était pas modifiée depuis 2013, nous avons réalisé une analyse similaire sur les essais publiés lors des 6 premiers mois de 2016.

2-3 Principaux résultats

Parmi les 716 articles identifiés lors de la recherche initiale, 112 ont été retenus.

Le délai entre la randomisation et l'évaluation du critère de jugement principal de l'essai était très souvent limité. En effet, parmi les essais évaluant le critère de jugement principal après une période donnée (et non à la sortie de la réanimation ou de l'hôpital), seulement 11% évaluaient ce critère au-delà de 30 jours après la randomisation.

Le classement dans les 6 catégories des 112 critères de jugement principaux montre que la catégorie des *patient-important outcomes* n'arrive qu'au troisième rang des critères utilisés (27/112, 24%). Les catégories des critères de jugement biologiques/physiologiques/radiologiques et des critères de jugement cliniques sont respectivement au premier et deuxième rang (33/112, 29% et 28/112, 25%). Le critère de jugement principal était plus souvent un *patient-important outcome* lorsque le sujet de l'étude portait sur le sepsis (8/21, 38%).

Parmi les 27 critères de jugement principaux classés dans la catégorie *patient-important outcomes*, la plupart étaient des critères de mortalité (21, 19%), alors que seulement 6 (5%) étaient critères de jugement rapportés par les patients évalués après le séjour en réanimation, comprenant la qualité de vie, la santé perçue et les capacités fonctionnelles.

Les résultats concernant le classement des 598 critères de jugement secondaires étaient très proches de ceux des critères de jugement principaux. Soixante-treize essais (65%) rapportaient au moins un *patient-important outcome* parmi l'ensemble des critères de jugement et seulement onze (10%) rapportaient au moins un critères de jugement rapportés par les patients évalués après le séjour en réanimation (qualité de vie, santé perçue et capacités fonctionnelles).

L'analyse des essais contrôlés randomisés publiés pendant les 6 premiers mois de 2016 a montré qu'il n'y avait pas eu d'évolution quant à la place des *patient-important outcomes* dans les essais randomisés en réanimation, puisque 25% de critères de jugement principaux étaient des *patient-important outcomes* sur ce premier semestre 2016 (contre 24% sur l'ensemble de l'année 2013).

2-4 Article 1 : Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review

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Soumis à Annals of Intensive Care

Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review

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ABSTRACT (350 words)

Background

Intensivists' clinical decision-making pursues two main goals for patients: to decrease mortality and to improve quality of life and functional status in survivors. Patient-important outcomes are gaining wide acceptance in most fields of clinical research. We sought to systematically review how well published randomized controlled trials (RCTs) report these patient-important outcomes in critically ill patients.

Methods

Literature search was conducted to identify eligible trials indexed from January to December 2013. Articles were eligible if they reported an RCT involving critically ill adult patients. We excluded phase II, pilot and physiological cross-over studies. We assessed study characteristics. All primary and secondary outcomes were collected, described and classified using 6 categories of outcomes including patient-important outcomes (involving mortality at any time on the one hand and quality of life, functional/cognitive/neurological outcomes assessed after ICU discharge on the other).

To detect a potential changing trend, we assessed the rate of patient-important outcomes as primary outcome in very recent RCTs (published between January 2016 and June 2016).

Results

Of the 716 articles retrieved in 2013, 112 RCTs met the inclusion criteria. Most common topics were mechanical ventilation (27%), sepsis (19%) and nutrition (17%).

Among the 112 primary outcomes, 27 (24%) were patient-important outcomes (mainly mortality, 21/27) but only 6 (5%) were patient-important outcomes besides mortality assessed after ICU discharge (functional disability=4; quality of life=2). Among the 598 secondary

outcomes, 133 (22%) were patient-important outcomes (mainly mortality, 92/133) but only 41 (7%) were patient-important outcomes besides mortality assessed after ICU discharge (quality of life=20, functional disability=14; neurological/cognitive performance=5; handicap=1; post-traumatic stress=1).

Seventy-three RCTs (65%) reported at least one patient-important outcome but only 11 (10%) reported at least one patient-important outcome besides mortality assessed after ICU discharge.

The rate of patient-important outcomes reported in our review of articles published in the first 6 months of 2016 was very similar (13/53 primary outcomes, 25%).

Conclusion

Patient important outcomes are rarely primary outcomes in RCTs in critically ill patients published in 2013. Among them, mortality accounted for the majority. This pattern was very similar in 2016. We promote the use of patient-important outcomes in critical care trials.

Keywords: Patient-important outcome, Critical care, Quality of life

BACKGROUND

The paternalistic model of patient care has also encompassed the field of research in critical care for many years. To change this paradigm, some clinicians and researchers recently advocated for “the patient at the center” of medical decision-making. They suggested recommending interventions, not when the magnitude of the effect was “clinically relevant” but when it was “patient important” (1). Other alternative terms for this paradigm shift have been suggested like “patient-oriented” (2) or “personal significant” (3) which encompass the patient’s family members or the individual involved in a community. The notion of “Patient-important”, however, sheds light on the individual clinical encounter and the preeminence of patient’s value and preferences within that encounter. In clinical research, a patient-important outcome has been previously defined as: “a characteristic or variable that reflect how a patient feels, functions or survives” (4,5).

The principal goal of implementing intensive care units (ICU) was to save the life of critically ill patients (i.e. decrease mortality). This goal has been reached in many clinical situations such as septic shock or acute respiratory failure, owing to progress in symptomatic and etiologic treatments of shock and in mechanical ventilation (6,7). Although this goal remains a major objective for intensivists, other priorities have emerged. In particular, the importance of assessing mean and long-term outcome in survivors has been underlined (8). Critical illness is indeed associated with a wide array of long-term sequelae (physical and psychical) that impact functional status and quality of life (9–13). To account for the patient perspective, clinical decision-making by ICU physicians now pursues the goal of improving mean and long-term outcomes in survivors in addition to increasing their chance of survival.

In clinical research, randomized controlled trials (RCTs) are considered the highest level of evidence to judge the true benefit of an intervention (14) and one of the most reliable sources

of evidence to guide clinical practice in the era of evidence-based medicine. As a matter of fact, the number of RCTs in critical care is steadily increasing. Publications in this field have evolved from physiological or case studies in the 70's (15,16) to evidence-based medicine in the 90's and following (17,18).

In addition to mortality, assessing mean to long-term outcomes (after ICU and hospital discharge) could help define the usefulness of an intervention, taking into account what might be relevant and advantageous for the patients (19).

Numerous questions around outcomes used in RCTs in critically ill patients led us to conduct this systematic review. The core question of this review was guided, however, by patients' priorities. We chose to define patient-important outcomes according to these patients' priorities (survival, quality of life, functional, cognitive and neurological performance assessed after ICU discharge) as it has been done in other fields such as diabetes (20).

The objective of this systematic review was to investigate if published randomized controlled trials (RCTs) in critically ill patients explore these patient-important outcomes.

METHODS

This is a systematic review. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement guidelines (21).

Outcome Classification

Our outcome classification was developed according to previous work on patient-important outcome in various medical domains (5,20,22).

A scientific committee (including 3 intensivists (SG, JDR, DD) and 1 methodologist (FT) particularly involved in designing and conducting RCTs in critically ill patients) established a classification of outcome categories relevant to ICU trials.

The experts identified 6 outcome categories:

- **Patient-important outcomes** that included two entities: on the one hand, mortality at any time and on the other, quality of life, functional/cognitive/neurological outcomes assessed after ICU discharge.
- **Clinical outcomes in ICU and hospital:** organ failure, complication/adverse outcomes (for instance: drug induced skin reaction or hypotension during renal replacement therapy), healthcare associated outcomes (nosocomial pneumonia, catheter related infections), delirium, clinical events (such as venous thromboembolism, myocardial infarction), pain (in ICU), anxiety (in ICU), conscience level, return to spontaneous circulation, muscle strength/circumference, sleep duration, National institute of health stroke score (NIHSS) (for acute phase of stroke), clinical response to antibiotics, dyspnea (in ICU), non-invasive ventilation tolerance.
- **Biological/Physiological/Radiological outcomes**, such as Brain Natriuretic Peptide (BNP), Neutrophil-Gelatinase-Associated Lipocalin (NGAL), total lung capacity, chest X-ray severity score.
- **Care provider decision-related outcomes:** e.g. mechanical ventilation duration, length of stay, antibiotic exposure, volume of fluid resuscitation, intubation or reintubation, number of gastric tubes for aspiration, sedation exposure (dose/time), renal replacement therapy, ICU readmission, non-invasive ventilation, tracheostomy, transfusion, use of a prokinetic agent, need for surgery, dose of local anesthesia, hospital discharge disposition.
- **Care-performance outcomes:** care procedure quality and noise/light exposure.
- **Other outcomes:** family satisfaction, physician/nurse or other provider satisfaction, cost/charges, withholding/withdrawal of care, patient judgment about his readiness to discharge, workload for staff team, compliance to a care protocol, medico-legal conflict.

Besides, for primary outcomes, we defined a “surrogate outcome” as an outcome measuring a substitute for some other variable (for example: a biomarker intended to substitute for a clinical endpoint) (4).

Article eligibility criteria

Articles were eligible if they met the following criteria: article published between January 2013 and December 2013; reporting an RCT involving critically ill adult patients (i.e. adults hospitalized in ICU); written in English.

We considered only the first report of the trial results and trial extension follow-up, i.e. we excluded articles reporting post-hoc analyses and sub-analyses of RCTs. Indeed, our aim was to focus on the RCTs’ initial objective. We also excluded phase II studies, pilot studies and physiological cross-over studies because studies at this stage of clinical research are expected to explore mainly physiological and feasibility outcomes.

To detect a potential changing trend, we performed an additional literature search with the same search strategy, article eligibility criteria, and outcome classification (see below) to assess the rate of patient-important outcomes as primary outcome in very recent RCTs (published between January 2016 and June 2016).

Search strategy and article selection

Main literature search (for the January 2013 to December 2013 period) was conducted on the July 16th 2014 in Medline (via Pubmed®) to identify eligible articles indexed between January 2013 and December 2013. The additional search for the first semester of 2016 was conducted on the September 12th 2016. The search strategy was the same for the 2 periods, and relied on two algorithms, one dedicated to articles indexed with Mesh terms, the other dedicated to articles not indexed (at the time of the search), using exclusively free text. Terms

related to intensive care were combined with terms related to RCTs. Details regarding the literature search strategy and the terms used are provided in the online supplement.

Two senior intensivists (SG and JM) independently screened the titles and abstracts for the eligibility criteria, to identify articles to be read in full text. Definite article selection was only achieved after examination of the full text confirmed that inclusion criteria were met.

Data Collection

A standardized extraction form (available from the corresponding author) was established from a literature review and a priori discussion. This extraction form was pretested by two authors (SG and JM) independently, in a set of 10 articles. This test enabled to identify items needing rewording to avoid any confusion. Disagreements were discussed with an epidemiologist (third author, FT), to ensure similar understanding. Once all litigious points were settled, two reviewers (SG and JM) independently extracted the following data from the selected articles (using the full text and the supplementary material): general data (funding source, geographical origin, topic, number of centers), methods (intervention assessed, study design, randomization design), quality assessment (by use of the Risk of Bias Tool (23)), trial characteristics (inclusion period, length of follow-up, number of randomized patients), and outcomes (time from randomization to assessment for primary outcome, type and characteristic of all outcomes, see paragraph above).

For all articles included in the systematic review, disagreements between the 2 reviewers (SG and JM) were resolved by consensus. In case of persistent disagreement, arbitration by a third reviewer (FT) settled the discrepancy.

Statistical analyses

A one-year time frame was chosen because it yielded a convenient study sample. Because of the significant lag in study indexation, the closest complete year available at the time of the literature search was 2013.

Continuous variables are described with median and interquartile range (IQR). Categorical variables are described with frequencies and percentages. Distribution of outcomes into the 6 categories (patient-important outcomes, clinical outcomes, bio/physio/radio outcomes, care provider decision related outcomes, care performance outcomes and others outcomes) is presented as radar plot. For primary and secondary outcomes, distribution is presented for all outcomes and according to 3 major topics.

Inter-reviewer agreement was measured by the kappa statistic for the following categorical variables: funding source, geographical origin, intervention assessed, unit of randomization and primary outcome category.

Statistical analysis was performed with GraphPad Prism 5 (GraphPad Software, San Diego, USA) and SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Selection of articles and inter-reviewer agreement

The electronic search identified 716 articles. Four hundred and eighty were excluded on the basis of the title and abstract, and 124 after reading the full-text. A total of 112 articles reporting RCTs in critically ill patients were finally included and analyzed (see Figure 1 for PRISMA flow diagram).

Inter-reviewer agreement before consensus for categorical variables was very good (24): the median kappa value was 0.89 [0.83-0.95] for funding source, 0.99 [0.96-1.00] for geographical origin, 0.83 [0.68-0.99] for unit of randomization and 0.95 [0.91-0.99] for

primary outcome category; and good for intervention assessed (median kappa 0.74 [0.65-0.82]).

Characteristics of the 112 RCTs

Table 1 summarizes RCTs characteristics. Mechanical ventilation (27%), sepsis (18%) and nutrition (17%) were the most common topics of these trials. Therapeutic strategy (41%), drug (33%) and device (11%) evaluation were the most frequent types of intervention.

Follow-up period was defined until a fixed time point for 44 (39%) RCTs (median [IQR]: 3[1-6] months of follow-up), until ICU discharge for 14 (12%) RCTs and until hospital discharge for 15 (13%) RCTs. Follow-up period was unclear for 39 (35%) RCTs.

Quality assessment

Quality of the trials using the risk of bias tool is provided in Figure 2. The absence of blinding of allocated intervention was the most frequent methodological component introducing a high risk of bias.

Primary Outcomes

Seventy-three (65%) RCTs assessed the primary outcome after a median [IQR] fixed time-point of 7 [2-28] days (from randomization) and only 13 (12%) assessed the primary outcome beyond 30 days (Figure 3). The other RCTs assessed the primary outcome at ICU discharge (n=25, 22%) or hospital discharge (n=9, 8%). Five (4%) did not specify the time from randomization to primary outcome assessment.

Among the 112 primary outcomes, 27 (24%) were patient-important outcomes. Most of them were mortality (21/27, 78%) and only 6/27 (22%) were quality of life,

functional/cognitive/neurological outcomes assessed after ICU discharge (functional disability=4; quality of life=2).

Among the 21 mortality outcomes 18 were assessed after a fixed time-point of 28 [28-60] days. The other 3 were assessed at ICU discharge. Among the 6 quality of life, functional/cognitive/neurological outcomes, 2 were assessed at hospital discharge and 4 after a fixed time-point (6 months, 12 months, 12 months, 14 months). Figure 4 shows the distribution of the 112 primary outcomes and according to the 3 major topics (mechanical ventilation, sepsis, nutrition). Besides, 45 (40%) primary outcomes were surrogate endpoints.

Secondary Outcomes

Among 598 secondary outcomes identified, 133 (22%) were patient-important outcomes. Most of them were mortality (92/133, 69%) and only 41 (31%) were quality of life, functional/cognitive/neurological outcomes assessed after ICU discharge (quality of life=20, functional disability=14; neurological/cognitive performance=5; handicap=1; post-traumatic stress=1).

Among the 92 mortality outcomes, 43 were assessed after a fixed time-point of 28 [28-90] days. The others were assessed at ICU discharge (n=26) or at hospital discharge (n=23). Among the 41 quality of life, functional/cognitive/neurological outcomes, 37 were assessed at a fixed time-point of 365 [319-380] days and 4 at hospital discharge.

Figure 5 shows the distribution of the 598 secondary outcomes and according to the 3 major topics (mechanical ventilation, sepsis, nutrition).

Trial characteristics associated to the presence of at least one patient-important outcome (primary or secondary)

Among the 112 RCTs, 73 (65%) reported at least one patient-important outcome (primary or secondary outcomes) but only 11 (10%) reported at least one quality of life, functional/cognitive/neurological outcomes assessed after ICU discharge. Characteristics of these RCTs are provided in Table 1.

Search for a changing trend in the rate of patient-important outcomes (first semester of 2016)

The electronic search identified 590 articles. A total of 53 articles reporting RCTs in critically ill patients were finally included in the study for the first semester of 2016.

Among the 53 primary outcomes, 13 (25%) were patient-important outcomes, which is very similar to the results over the year 2013 (27/112, 24%). Most of them were mortality (10/13, 77%).

DISCUSSION

We found that, during the one-year survey period of RCTs performed in critically ill patients, a minority of outcomes used in these RCTs were patient-important outcomes. They accounted for 24% and 22 % of primary and secondary outcomes, respectively. Mortality accounted for the vast majority of reported patient-important outcomes, whereas other patient-important outcomes (such as quality of life, functional/cognitive/neurological outcomes assessed after ICU discharge) were scarcely used (7% of all outcomes). Moreover, only 10% of surveyed RCTs reported at least one patient-important outcome besides mortality (quality of life, functional/cognitive/neurological outcomes assessed after ICU discharge). The same figures were evidenced in the very recent literature. This is at striking contrast with clinical decision-making of ICU physicians, which is felt to be in line with these crucial outcomes. In addition, we were cautious to retain only those RCTs for which patient-important outcomes were reasonably expected. Indeed, studies for which patient-important outcomes were less likely to

be present (phase II studies, pilot studies and physiological cross-over studies) were not included.

Our study is the first to explore the place of patient-important outcomes and how well they are reported in RCTs in critically ill patients. We derived the definition of patient-important outcome for critically ill patients from the definition used in other fields (5,20,22). Mortality is obviously essential, and we considered that quality of life, functional/cognitive/neurological outcomes assessed after ICU discharge also qualified for patient-important outcome. Indeed, the potential adverse consequences of an ICU stay are best evaluated after ICU discharge and even more after hospital discharge since critical illness is associated with long-term sequelae. Survivors of critical care experience profound changes in their lives because of many forms of deficit in one or more domains (25) of physical (26,27), psychological (13,28,29) or cognitive functioning (29–32). These numerous symptoms led to define the new entity of “post-intensive care syndrome” (33).

To perform this systematic review, we developed an outcome classification relevant to the context of critical care, involving 6 categories (patient-important outcomes, clinical outcomes in ICU and hospital, Biological/Physiological/Radiological outcomes, Care provider decision-related outcomes, Care performance outcomes and Others). A systematic review is the first step to establish a core outcome set and our outcome classification could help researchers to clarify the place of patient-important outcomes in core outcome sets for future RCTs in critically ill patients. To date there is no taxonomy of outcomes studied in critically ill patients, nor core outcome set. This may cause inconsistencies in outcome reports and difficulties in comparing these outcomes across studies and to combine them in systematic reviews and meta-analyses (34). With the aim to facilitate the development and application of

agreed standardized sets of outcomes, the Core Outcome Measures in Effectiveness Trials (COMET) initiative was initiated in 2010 (35). In the field of critical care, the Core Outcomes in ventilation Trials (COVenT) is in progress (36). This systematic review can be the first step to develop other core outcome sets in other topics of critical care and to establish a core outcome set involving patients' opinion for future RCTs.

An inherent limitation of a systematic review of published trials is that it is performed at a given period (here 2013). The search led to identify 112 eligible RCTs, which provides a very large panel of ICU trials and thus robust information on the prevalence of patient-important outcomes in RCTs in critically ill patients. Many systematic reviews rely issues on a 1 year-literature search (37,38). Our goal was to capture the most recent practices in trials as the literature on patient-important outcomes in other medical field and the growing interest for the patients' perspective may have had an impact. Our hypothesis was confirmed by our analysis of most recently published RCTs: patient-important outcomes were used in the same low proportions as in the 2013 sample.

Patient-important outcomes are gaining wide acceptance in some fields of clinical research (39–41). Additionally, a recent survey from 2,036 patients with diabetes showed that most of them (>75%) chose patient-important outcomes rather than HbA1c as their first choice for a trial primary outcome (42). Patients understand the reality of their condition and disease's impact on their lives better than physicians can do (43). James Lind Alliance in the United Kingdom (44,45) and the Patient Centered Outcome Research Institute in the United States (46–49) showed the mismatch between questions patients and clinicians needed an answer for on the one hand and those that were investigated by researchers on the other. This led some opinion leaders to call for a patient revolution (50). Patients who survive after a critical illness

may experience many sequelae after ICU or hospital discharge. In our study only 10% of RCTs reported at least one non-mortality patient-centered outcome assessed after ICU discharge. It seems therefore desirable that more long-term outcomes be assessed in ICU studies.

Reasons explaining this small percentage of RCTs assessing patient-important outcomes and in particular the impressive scarcity of outcomes assessed after ICU discharge are diverse. One of them is the difficulty to ascertain mean and long term follow-up of patients. The preference of researchers and funding agencies for rapidly obtained results favors short-term outcomes. This could be a shortcoming since paradoxical short- and long-term effects after certain interventions have been described (51,52). For instance, after acute myocardial infarction flecainide decreased arrhythmias but has been associated with increased mortality (51). In critical illness, growth hormone improved nitrogen balance but has been also associated with increased mortality (53). Moreover, many proposed short-term endpoints in critical care have not been formally evaluated for surrogacy (54) precluding any strong conclusion on the effect on patient-important outcomes. For example, acute organ dysfunction in ICU does not appear to have significant long-term implications for patient-important outcomes (55). In our systematic review, we found that 40% of primary outcomes were surrogate endpoints.

To promote the assessment of patient-important outcomes, patients' follow-up should be extended but this can be hampered by logistical issues (organization of phone call, medical consultation, etc..) which can considerably increase the costs of the study. As a result, we found that patients' follow-up was short since only 12% of trials assessed primary outcomes beyond 30 days from randomization. Patient-important outcomes were initially promoted to evaluate outcomes of chronic diseases (20,22) for which patients' follow-up is easier to

perform because the patient is cared for by the same medical team. This situation is quite different for critically ill patients who are often cared for by a different team after ICU discharge. The advent of post-ICU consultation (56) could foster a better assessment of patients-important outcomes by intensivists and researchers in the field.

Additionally, lengthy technical questionnaires are usually used to assess patient-reported outcomes (i.e., quality of life or functional status) after ICU discharge. This often leads to a high proportion of non-responders that renders interpretation more difficult (57). The question of the applicability to the ICU setting of the tools used is also raised by ICU experts: “Are existing instruments suitable for capturing important nuances of post-ICU sequelae or should disease-specific instruments be captured” (8).

The decisions intensivists make at the bedside aim at both saving lives and preserving - at best - their patients’ prior quality of life. Medical research and especially RCTs should help them to better evaluate the efficacy of their interventions (drug administration, therapeutic strategy implementation or device use) on these relevant issues.

Our results indicate that outcomes of many RCTs remained too often centered on physiological criteria (oxygenation or hemodynamic stabilization for instance) or assessed mortality as sole outcome of importance for patients. This has two pitfalls: quality of life of survivors is not assessed, and given the noticeable improvement of vital prognosis in a number of ICU situations (ARDS for example), many interventional studies using mortality as primary outcome have been negative in recent years, mandating the use of alternative outcome measures, such as patient-important ones (54,58,59).

Conclusion

Our study shows that only a small number of primary outcomes measures in recent RCTs performed in the ICU are patient-important outcomes. To better address patient needs, researchers should take the crucial post ICU period into account in the design of future RCTs. This is one of the challenges for future ICU research. This paradigm shift would be in the interest of patients.

LIST OF ABBREVIATIONS

ICU: Intensive Care Units

RCT: Randomized Controlled Trial

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

ARDS: Acute Respiratory Distress Syndrome

NIHSS: National institute of health stroke score

BNP: Brain Natriuretic Peptide

NGAL: Neutrophil-Gelatinase-Associated Lipocalin

COMPETING INTERESTS

None of the authors have any competing interests in the manuscript

FUNDING

None

AUTHORS' CONTRIBUTIONS

StG, JM, TB and FT performed the data extraction; SyG and ED performed the literature search; BP performed statistical analysis; StG, JM, J-DR, DD and FT wrote and reviewed the manuscript.

TABLE

Table 1: Characteristics of RCTs in critically ill adult patients

CHARACTERISTIC	All RCTs No. (%)	RCTs reporting at least one patient- important outcome No. (%)	RCTs reporting at least one patient-important outcome besides mortality No. (%)
Total –n	112	73	11
Funding			
Public	57 (51)	42 (57)	6 (54)
Industry	11 (10)	8 (11)	
Both public and private	16 (14)	10 (14)	3 (27)
Not reported or unclear	28 (25)	13 (18)	2 (18)
Geographic area			
Europe	46 (41)	34 (47)	4 (36)
Asia	37 (33)	19 (26)	1 (9)
North America	20 (18)	16 (22)	2 (18)
Oceania	11 (10)	9 (12)	4 (36)
South America	10 (9)	8 (11)	1 (9)
Africa	5 (4)	5 (7)	
<i>International (>1 country)</i>	18 (16)	18 (25)	3 (27)
Number of center(s)			
Monocenter	63 (56)	33 (45)	5 (45)
Multicenter	45 (40)	38 (52)	5 (45)
Unclear	4 (4)	2 (3)	1 (9)
Sample size			
<50	32 (29)	16 (22)	4 (36)
50-100	21 (19)	14 (19)	
100-150	11 (10)	5 (7)	
150-500	27 (24)	20 (27)	3 (27)
>500	21 (19)	18 (25)	4 (36)
Topic of the study *			
Mechanical ventilation	30 (27)	16 (22)	
Sepsis	21 (19)	19 (26)	1 (9)
Nutrition	19 (17)	14 (19)	3 (27)
Infection	18 (16)	10 (14)	
Hemodynamics	6 (5)	4 (5)	
ARDS	9 (8)	7 (10)	1 (9)
Cardiac arrest	6 (5)	4 (5)	1 (9)
Trauma	6 (5)	3 (4)	1 (9)
Sedation	3 (3)	1 (1)	
Acute kidney injury	4 (4)	3 (4)	
Pain	4 (4)	2 (3)	1 (9)
Neurocritical care	1 (1)		
Hematological issue	3 (3)	2 (3)	
Rehabilitaion/Physical and/or cognitive therapy	2 (2)		2 (18)
Metabolic disorder	1 (1)		
Burns	1 (1)	1 (1)	
ECMO	1 (1)	1 (1)	
Electric muscle stimulation	1 (1)		1 (9)
Music	1 (1)		1 (9)
Type of intervention			
Therapeutic strategy	46 (41)	32 (44)	9 (82)
Drug	37 (33)	24 (33)	1 (9)

Device	13 (12)	7 (10)	
Monitoring	3 (3)	1 (1)	
Diagnostic strategy	4 (4)	4 (5)	
Other	9 (8)	5 (7)	1 (9)
Unit of randomization			
Patient	102 (91)	67 (92)	10 (91)
Service	5 (4)	3 (4)	
Time	2 (2)	1 (1)	
Other	3 (3)	2 (3)	1 (9)
Type of trial			
Superiority	108 (96)	70 (96)	11 (100)
Equivalence or non-inferiority	4 (4)	3 (4)	
Follow-up			
Fixed time point		41 (56)	8 (73)
<i>Median months [IQR]</i>		3 [1-9]	12 [6-12]
ICU		7 (10)	
Hospital		12 (16)	3 (27)
Unreported		13 (18)	

The numbers in parentheses mean the percentage; ECMO: extra-corporeal membrane oxygenation.

* One study could have more than one topic

A study can appear in more than one row for geographic area

FIGURES

Figure 1: PRISMA flow diagram

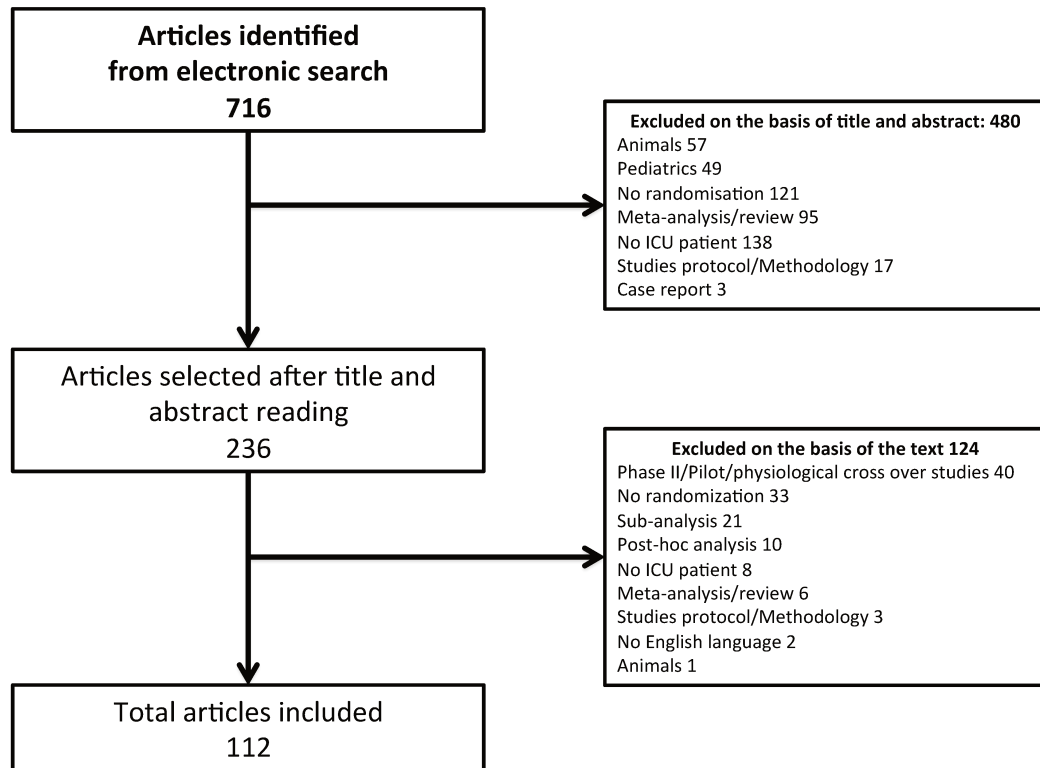


Figure 2: RCTs quality assessment by Risk of Bias Tool (16)

Legend: Methodological quality of the trials included in the systematic review assessed by 6 points: Random sequence generation, allocation concealment, blinding of allocation intervention, incomplete data adequately addressed, free of suggestion selective outcome reporting, other problems.

Horizontal axis represents the ratio (%) distribution among “low risk of bias” (green), “high risk of bias” (red) and “unclear risk of bias” (yellow).

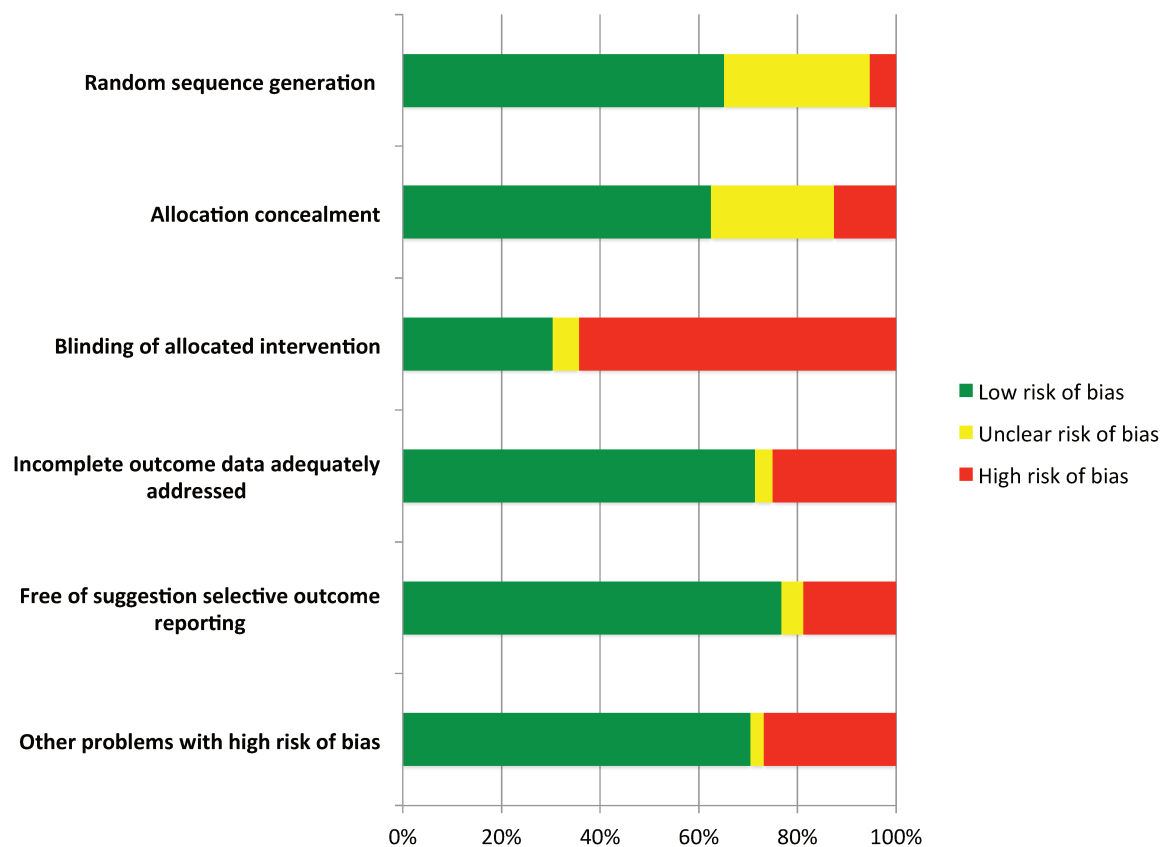


Figure 3: Time from randomization to assessment of primary outcome

Legend: This figure represents the distribution of the time from randomization to assessment of primary outcome for the 73 RCTs that assessed the primary outcome after a fixed time-point.

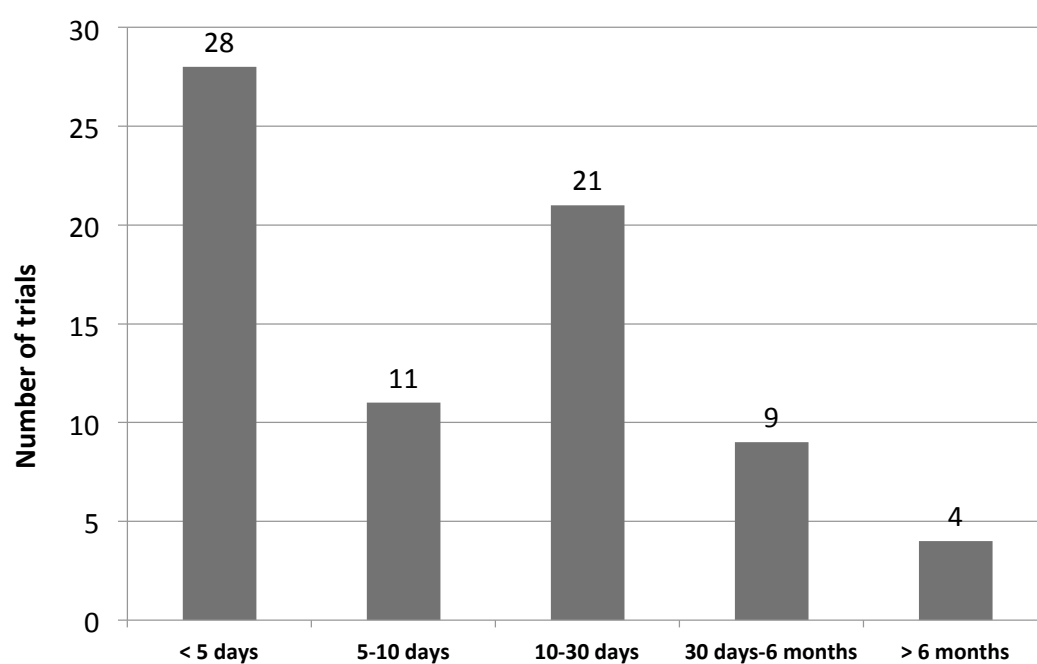


Figure 4: Distribution of primary outcomes

Legend:

4a: Distribution of 112 primary outcomes

Percentage of primary outcomes by outcome category

4b: Distribution of primary outcomes according to 3 major topics (mechanical ventilation, sepsis and nutrition)

Percentage of primary outcomes by outcome category.

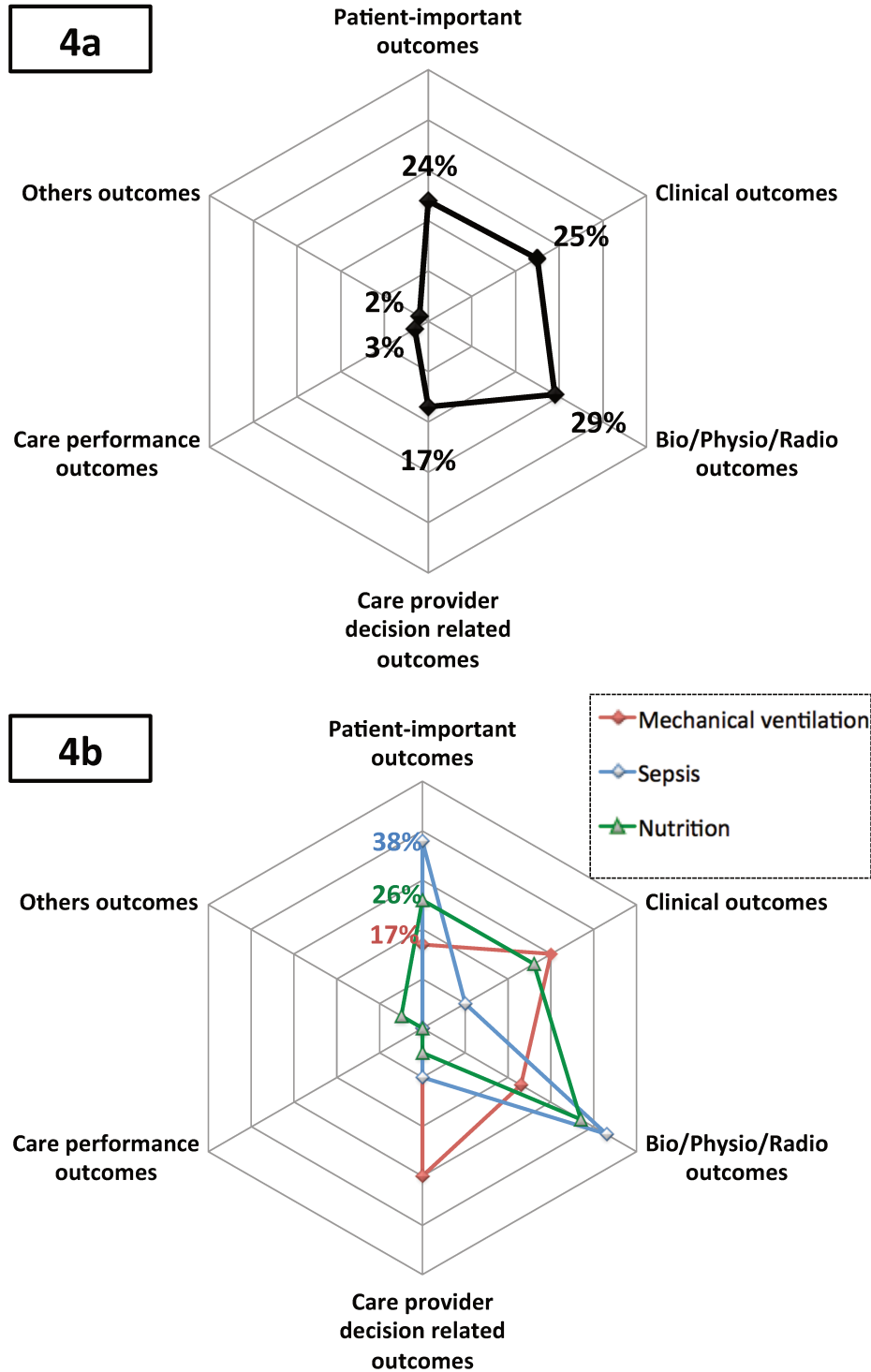


Figure 5: Distribution of secondary outcomes

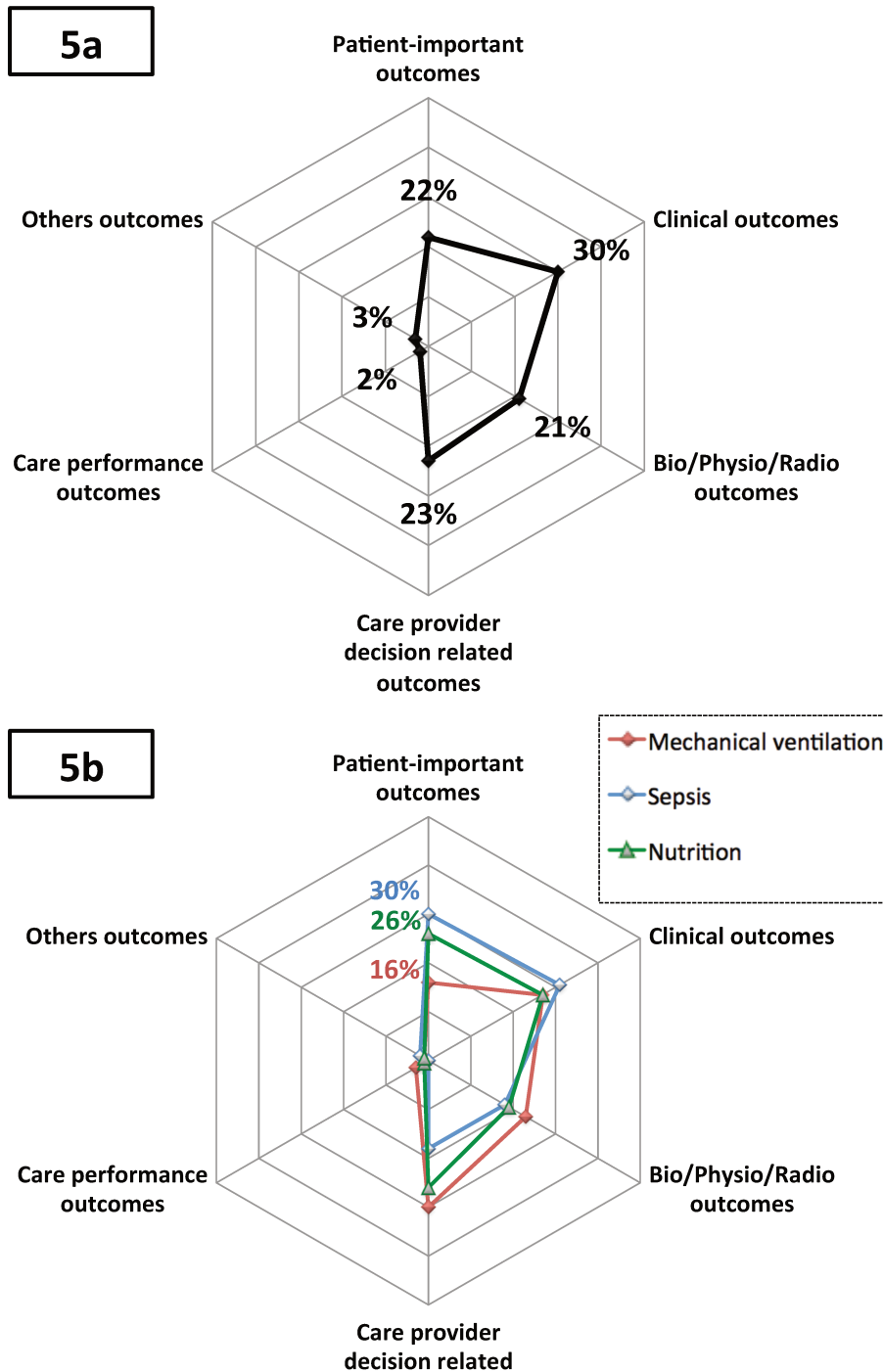
Legend:

5a: Distribution of 598 secondary outcomes

Percentage of secondary outcomes by outcome category

5b: Distribution of secondary outcomes according to 3 major topics
(mechanical ventilation, sepsis and nutrition)

Percentage of secondary outcomes by outcome category



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3/ PLACE ET INFLUENCE DES DECISIONS LIMITATION(S) OU D'ARRÊT(S) DES THERAPEUTIQUES DANS LES ESSAIS CONTROLES RANDOMISES EN REANIMATION

3-1 Objectifs

Nos objectifs étaient :

1. De décrire le *reporting* des décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives dans les essais contrôlés randomisés en réanimation ayant un critère de jugement de mortalité.
2. D'évaluer l'impact d'un déséquilibre en termes de décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives entre les 2 bras d'un essai contrôlé randomisé utilisant la mortalité comme critère de jugement.

3-2 Méthodologie

Il s'agit d'une étude ancillaire de la revue systématique présentée dans l'article précédent. Dans les 112 articles rapportant en 2013 un essai randomisé en réanimation et sélectionnés dans notre revue systématique, nous avons sélectionné les essais ayant au moins un critère de jugement (principal ou secondaire) de mortalité. Puis, nous avons recherché si les décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives étaient rapportées au cours du suivi des patients inclus, et lorsque c'était le cas, quelles données étaient rapportées.

En parallèle à ce travail de revue systématique, nous avons réalisé une étude de simulation afin d'évaluer l'impact d'une prise de décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives différentielle entre les 2 bras de l'essai (expérimental versus contrôle) sur les résultats en termes de mortalité. Pour cela, nous avons pris l'exemple d'un essai incluant 1000 patients et dont la mortalité globale attendue à J60 était de 50% (67). Nous avons fait varier 3 paramètres :

1. L'effet du traitement évalué sur la mortalité (absence d'effet, effet protecteur du bras expérimental, ou effet délétère du bras expérimental)
2. L'effet du groupe de traitement sur la prise de décision de limitation(s) des thérapeutiques actives (absence d'effet, décision plus tardive dans le bras expérimental, ou décision plus précoce dans le bras expérimental).
3. La fréquence des décisions de limitation(s) des thérapeutique(s) actives

3-3 Principaux résultats

Parmi les 65 articles sélectionnés, 6 (9%) rapportaient le taux de décision de limitation(s) ou d'arrêt(s) des thérapeutiques actives au cours du suivi.

Dans ces 6 articles, le sujet des décisions de limitation(s) thérapeutique(s) était abordé systématiquement dans la section résultats et une seule fois dans la section méthode. Une seule étude (portant sur le pronostic neurologique de la mort subite) utilisait un protocole détaillé de prise de décision de limitation(s) ou d'arrêt(s) des thérapeutiques actives dont l'objectif était de standardiser ces prises de décision.

Parmi les 6 articles rapportant le taux de décision de limitation(s) ou d'arrêt(s) des thérapeutiques actives, une seule étude précisait le délai entre la randomisation et cette décision. Seuls 4 essais rapportaient ce taux par bras (et 2 globalement). Aucune étude ne rapportait le taux ou le délai de ces décisions au-delà de la date d'évaluation du critère de jugement mortalité.

L'étude de simulation a permis de montrer que lorsque les décisions de limitation(s) thérapeutique(s) étaient prises de façon plus tardive dans le groupe expérimental, l'intervention pouvait apparaître protectrice alors même qu'il n'existait pas de réel effet sur la survie. Nous avons proposé certaines méthodes d'analyse permettant de s'affranchir du biais potentiel lié à un déséquilibre entre les deux bras d'un essai dans la prise de décision de limitation(s) thérapeutique(s). Une première façon de faire est de réaliser un ajustement, en considérant la

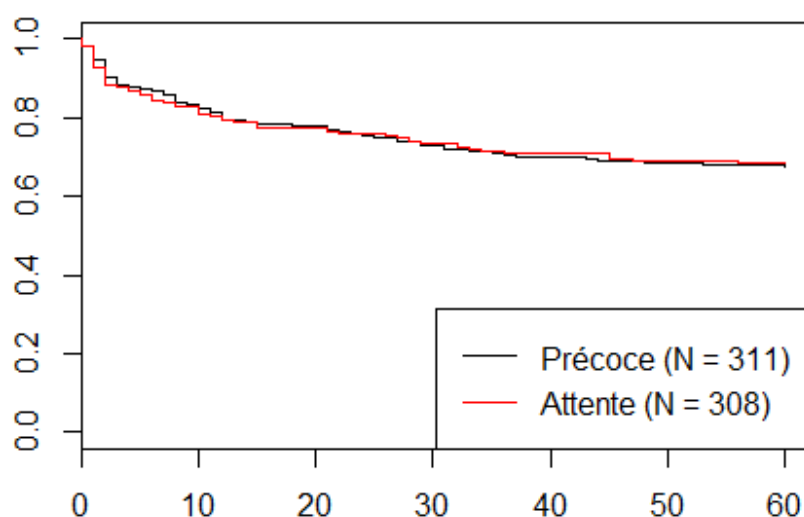
décision de limitation(s) thérapeutique(s) comme une variable dépendant du temps (la décision de limitation(s) thérapeutique(s) est prise en compte comme un facteur confondant). Une seconde façon de faire est de considérer les décisions de limitation(s) thérapeutique(s) comme des censures. Nous avons appliqué ces deux méthodes pour l'analyse de la survie globale (critère de jugement principal) de l'essai AKIKI (67) (Figure 5).

Analyse du critère de jugement principal (survie à J60) de l'essai AKIKI :

- en censurant le patient dès lors qu'une prise de décision de limitation(s) ou d'arrêt(s) des thérapeutiques survient. HR = 0,98 CI95% [0,73 ; 1,33], p= 0,92. (représentation de Kaplan-Meier, Figure 5)
- en prenant en compte la décision comme une variable dont la valeur dépendant du temps : HR = 0.97 CI95% [0.78 ; 1.22]

Le résultat ainsi présenté n'est pas différent du résultat simple ne prenant pas en compte le paramètre « prise de décision de limitation(s) ou d'arrêt(s) des thérapeutique(s) ».

Figure 5 : Analyse du critère de jugement principal (survie à J60) de l'essai AKIKI en censurant le patient dès lors qu'une prise de décision de limitation(s) ou d'arrêt(s) des thérapeutiques survient.



Compte tenu des résultats de ce travail, 4 points pourraient être recommandés :

- L'utilisation de protocoles standardisés de décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives. Cette proposition peut sembler ambitieuse mais un essai inclus dans notre revue systématique utilisait un tel protocole standardisé (68). Les auteurs de ce travail n'ont pas rapporté de difficulté à sa mise en place lors de l'étude.
- Décrire le taux de décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives dans chacun des bras de l'essai.
- Décrire le délai entre la randomisation et la prise de décision de limitation(s) ou d'arrêt(s) des thérapeutiques actives dans les 2 bras. Sur ce point, il serait également souhaitable de rapporter le nombre de ces décisions au-delà du temps d'évaluation du critère de

jugement mortalité. Ainsi, un déséquilibre entre les 2 bras apparaissant après le moment de l'évaluation du critère de jugement mortalité serait très évocateur d'un biais de performance.

- Rapporter une analyse de sensibilité permettant de s'assurer de la robustesse des résultats si les résultats sont concordants avec l'analyse principale (une forte modification du *hazard ratio* pourrait évoquer un biais de performance). Deux approches pourraient être alors proposées : un ajustement ou une censure dès lors qu'une prise de décision de limitation(s) thérapeutique(s) survient.

3-4 Article 2: Withdrawal of life support therapies reporting in randomized controlled trial in critically ill patients: a systematic review and statistical simulation study

Jonathan Messika*, **Stéphane Gaudry***, Florence Tubach, Sylvie Guillo, Didier Dreyfuss, David Hajage**, Jean-Damien Ricard**

Article en rédaction

Withdrawal of life support therapies reporting in randomized controlled trials in critically ill patients: a systematic review and a statistical simulation study

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INTRODUCTION

ICU physicians often have to take decisions to withdraw or withhold non-beneficial treatments in order to preserve their patients dignity in the end-of-life care (1). Withholding and withdrawal of life support therapies (W-WLST) is a rather old concept, as it has been reported to be taken in intensive care units (ICUs) since the late 70's (2). In recent large multicenter observational studies on the subject (3–5), approximately 10% of all the patients hospitalized in ICUs were concerned by W-WLST decisions. These decisions have considerable consequences since death in the ICU is preceded by W-WLST decisions in 26 to 59% of cases (6,7). It therefore appears that decisions to withdraw or withhold treatments could hasten patients' death. In other words, the timing of W-WLST decision might affect, in some cases, patient's length of ICU survival. Almost two thirds (63.6%) of patients in whom a do-not-resuscitate (DNR) order was written in the ICU were not discharged from ICU alive, with a mean ICU length of stay of 3 days. This figure rose to 85% when looking at hospital discharge (2). By contrast, ICU and hospital deaths in patients without DNR orders were significantly lower (4.3 and 10.7% respectively) (2). Nevertheless, some patients in whom W-WLST decisions have been taken might be discharged alive from the ICU (5), and die rapidly after ICU discharge. A recent retrospective analysis (7) of a database of 400,129 US ICU admissions reported the time to death after ICU W-WLST decision, in a subgroup of patients discharged alive. The median time from DNR to ICU discharge was 24h (0-48h) and from ICU discharge to death was 2h (1-4h).

RCTs involving critically ill patients, mortality is frequently used as primary or secondary outcome, which makes critical the issue of W-WLST in these RCTs as W-WLST decisions could hasten patients' death (i.e. it modifies the risk of death) (3, 5, 6), .

Hence, we focused our researches on 2 questions:

First, as W-WLST decisions may impact mortality, we questioned their reporting in randomized controlled trials (RCTs) with mortality as primary outcome in critically ill subjects.

Secondly, we hypothesized that an imbalance on W-WLST decisions between 2 arms of an RCT could lead to misinterpretation of a mortality outcome. Such imbalance could have 2 explanations: 1/ a difference in the real effectiveness between the 2 interventions (through the impact of the interventions on W-WLST decisions); 2/ and/or a performance bias (*i.e.* systematic differences in patients care outside the study treatment) very likely in open-label trials. We therefore sought to investigate how W-WLST decisions might impact the results of a randomized ICU study.

METHODS

Methods of the systematic review and of the simulation study are addressed separately.

1. Systematic review of RCT involving critically ill adult patients

For this systematic review, we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement guidelines (8). We performed an ancillary study of a systematic review on outcomes criteria in RCTs in critically ill patients. Detailed methods were described in detail in this publication.

Eligibility Articles Criteria

Articles were eligible if they met the following criteria: article published from January 2013 to December 2013; reporting a RCT involving critically ill adult patients (*i.e.* adults hospitalized in ICU); written in English.

We considered only the first report of the trial results and did not consider trial extension follow-up. We also excluded phase II studies, pilot studies and physiological crossover studies.

For this ancillary study, we considered only RCTs with mortality as primary or secondary outcome.

Search strategy and article selection

Literature searches were conducted on the 16th of July 2014 in Medline (via Pubmed®) to identify eligible articles indexed from January 2013 to December 2013. The search strategy relied on two algorithms, one dedicated to articles still indexed with Mesh terms, the other dedicated to articles not indexed (at the time of the search), using exclusively free text. Terms related to intensive care were combined with terms related to RCTs. Details regarding literature search strategy and used terms are provided in the online supplement.

Two senior intensivists (SG and JM) independently screened the titles and abstracts regarding the eligibility criteria (excluding “mortality as primary or secondary outcome”), to identify articles to be read in full text. Then, reading of the full text allowed determining whether the article definitely met the all inclusion (including “mortality as primary or secondary outcome”).

Data Collection

Data collection was performed using a standardized extraction form (available from the corresponding author). Two reviewers (SG and JM) independently extracted the data from the selected articles.

Special attention was paid to identify if W-WLST were recorded during the patient’s follow-up. General data on the trial were collected (geographic area, sample size, topic of the study,

type of intervention, type of trial, the overall quality assessed by risk of bias tool, the survival rate in each arm). Specific data on W-WLST were extracted: section (abstract, methods, results and discussion) in which W-WLST was reported, number and percentage of patients affected by W-WLST (for each arm), reporting of the timing of W-WLST, even after the time point for the primary endpoint, their type (withholding or withdrawal) and if they were followed by death. Corresponding authors of the trials reporting W-WLST were contacted by email in order to clarify if a pre-specified protocol for W-WLST was used for such decisions. If yes, they were asked to communicate it.

Statistical analyses

Continuous variables are described by median and interquartile range (IQR). Categorical variables are described with frequencies and percentages. Statistical analysis was performed with GraphPad Prism 5 (GraphPad Software, San Diego, USA) and SAS version 9.3 (SAS Institute Inc, Cary, NC).

2. Simulation study

To illustrate the potential impact of W-WLST decisions on the results of an RCT, we considered a study evaluating the effect of an experimental intervention compared to a controlled intervention on the overall survival (*i.e.* the outcome of interest is the time to death). During subjects' follow-up, a W-WLST decision may occur, which modifies (and increases) the risk of death (figure 1). In this study, all subjects are censored at day 60. The recommended approach to analyze this type of censored outcomes is to use a survival analysis. But several methods could be considered, accounting or not for the W-WLST status during the follow-up. In this simulation study, four methods are compared.

- 1) A “simple” approach, considering the time to death only, ignoring the occurrence of a W-WLST decision during follow-up;
- 2) A “composite” approach, considering the time to “death or W-WLST decision”, *i.e.* the time to the occurrence of the first of these two events. This approach does not evaluate the overall survival, but a composite outcome.
- 3) A “censored” approach, considering the time to death, but censoring the follow-up at the time of W-WLST if a W-WLST decision occurred. This approach considers the occurrence of a W-WLST decision before death as a competing event.
- 4) An “adjusted” approach, considering the time to death, but taking into account the W-WLST occurrence as a time-varying exposure. This approach considered the W-WLST status as a confounding factor.

Simulation setup

Definitions

In a randomized study with N subjects, let E be an indicator variable denoting the treatment status ($E = 1$ for subjects randomized in the experimental arm, $E = 0$ otherwise), D be an indicator variable of the event of interest ($D = 1$ if subject died during the follow-up period, $D = 0$ otherwise) and Z an indicator variable of the W-WLST decision ($Z = 1$ if a W-WLST occurred during the follow-up period, $Z = 0$ otherwise). Finally, let t be the observed follow-up time, t_d the theoretical times to death and t_z the theoretical time to W-WLST decision.

Data generating process

We used a data generating framework generating survival times to simulate Cox proportional hazards models with time-varying covariates (9). Herein, there is only one dichotomous time-varying covariate with at most one change from unexposed to exposed (the W-WLST status Z), and one time-invariant covariate (the treatment status E).

First, for each subject, the exposure allocation E was randomly drawn from a Bernoulli distribution $E \sim B(0.5)$.

A W-WLST decision time t_z with exponential distribution was generated as follows:

$$t_z = -\log(U_z)/(\lambda_z \exp(\beta_z E))$$

where U_z is drawn from a uniform distribution $U(0,1)$, λ_z is a constant baseline hazard function, and β_z is the effect of E on the time to W-WLST (i.e. β_z is the theoretical log hazard ratio associated with the treatment status on the W-WLST decision). Thus, t_z denote the time at which the W-WLST status (a time-varying exposure) changes from unexposed ($Z = 0$) to exposed ($Z = 1$). λ_z was selected so that the rate of W-WLST decision among the simulated sample is fixed at a desired proportion r_z . If β_z differs from 0, W-WLST decision occurs more rapidly in the experimental arm ($\beta_z > 0$) or more rapidly in the control arm ($\beta_z < 0$), which mimic a situation where the W-WLST decision process is different according to the randomization arm.

Then, a death time t_d with exponential distribution was generated as follows:

$$t_d = -\log(U_d)/[\lambda_d \exp(\beta_d E)] \text{ if } -\log(U_d) < \lambda_d \exp(\beta_d E) t_z,$$

$$t_d = [-\log(U_d) - \lambda_d \exp(\beta_d E) t_z + \lambda_d \exp(\beta_d E + \delta) t_z]/[\lambda_d \exp(\beta_d E + \delta)] \text{ if } -\log(U_d) \geq \lambda_d \exp(\beta_d E) t_z,$$

where U_d is drawn from a uniform distribution $U(0,1)$, λ_d is a constant baseline hazard function, β_d is the effect (log hazard ratio) of E on the time to death (protective effect of the experimental arm if $\beta_d < 0$), and δ the effect (log hazard ratio) of the W-WLST decision on the time to death. λ_d was chosen to achieve a desired censoring rate r_c in the simulated sample. Finally, the observed time to death outcome was obtained with the following decision rules:

$$D = 0, t = 60 \text{ if } t_d > 60,$$

$$D = 1, t = t_d \text{ if } t_d \leq 60.$$

$t_z < t$ means that a W-WLST decision occurred during the follow-up of the subject ($Z = 0$ before t_z , $Z = 1$ after t_z), otherwise no W-WLST decision occurred before death or day 60 ($Z = 0$ during the entire follow-up of the subject).

Simulation parameters

In all simulations, the following parameters were fixed:

$N = 1000$ (the sample size);

$r_c = 50\%$ (the censoring rate in the sample, meaning that the theoretical overall survival is 50% at day 60);

$\delta = \log(4)$ (the effect of Z on the risk of death);

Several simulation scenarios were explored, defined according to the following parameters:

$r_z \in \{20\%, 40\%\}$ (the proportion of W-WLST decision in the sample);

$\beta_z \in \{\log(1/1.5), \log(1), \log(1.5)\}$ (the effect of the treatment status E on the risk of W-WLST decision);

$\beta_d \in \{\log(1/2), \log(1/1.5), \log(1/1.2), \log(1/1.1), \log(1), \log(1.1), \log(1.2), \log(1.5), \log(2)\}$ (the effect of the treatment status E on the risk of death);

Evaluation of the treatment effect

All statistical methods described in Section 1 were applied to each simulated dataset.

a) Simple approach

The “simple” approach consists in applying the Cox proportional hazards model given by the following equation:

$$\lambda(t) = \lambda_0(t)\exp(\hat{\beta} E).$$

Thereafter, the “simple” method will be considered as the reference method to evaluate the impact of W-WLST occurrence on the estimation of the treatment effect $\hat{\beta}$, as this is the approach used in the majority of the RCT evaluating the overall survival.

b) Composite approach

The “simple” approach consists in applying the Cox proportional hazards model given by the following equation:

$$\lambda(t') = \lambda_0(t') \exp(\hat{\beta} E)$$

where $t' = \min(t, t_z)$ is the time to the occurrence of the first event among W-WLST decision and death.

c) Censored approach

The “censored” approach consists in applying the Cox proportional hazards model given by the following equation:

$$\lambda(t) = \lambda_0(t) \exp(\hat{\beta} E)$$

using a time of censoring equal to $\min(t_z, 60)$.

d) Adjusted approach

The “adjusted” approach consists in applying the Cox proportional hazards model given by the following equation:

$$\lambda(t) = \lambda_0(t) \exp(\hat{\beta} E + \hat{\delta} Z(t))$$

In this model, the treatment effect estimation is adjusted on the W-WLST status considered as a time-varying variable ($Z(t) = 0$ if $t < t_z$, $Z(t) = 1$ if $t \geq t_z$).

e) Performance criteria

We performed $B = 1,000$ simulations per scenario. Results were assessed in terms of:

bias of the treatment effect estimation: $\sum_{b=1}^B (\hat{\beta} - \beta_d) / B$,

and coverage: proportion of times β_d is enclosed in the 95% confidence interval of β_d estimated from the model.

Software

All simulations and analyses involved use of R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Selection of the trials and characteristics

Selection and characteristics of the trials were previously described elsewhere (Ref: PIO). Among 716 trials identified, 112 were included and analyzed in our first systematic review on outcome criteria. Among these 112 trials, 65 reported at least one mortality outcome (as primary or secondary outcome) (see Figure 2 for PRISMA flow diagram).

Characteristics of the 65 RCTs

Table 1 summarizes RCT characteristics. Sepsis (26%) Mechanical ventilation (23%), and nutrition (17%) were the most common topics of these trials. Therapeutic strategy (40%), drug (35%) and device (11%) evaluation were the most frequent types of intervention.

Quality of the 65 trials using the risk of bias tool is provided in the supplementary appendix. The absence of blinding of allocated intervention was the most frequent methodological component introducing a high risk of bias (40/65, 62%).

Trials reporting W-WLST

Six trials (6/65, 9%) reported W-WLST decisions during subjects' follow-up (Table 2). Only one RCT detailed the timing and the proportion of W-WLST decision in each arm. (10). For the five other RCTs, the timing of W-WLST with regard to the time of assessment of the primary endpoint was not detailed. The type of W-WLST (withholding or withdrawal) was detailed in 5 RCTs (and were all withdraw decisions); and only W-WLSD decisions followed by death were reported in 3 RCTs.

These 6 trials reporting W-WLST decisions were published in general journals (3 RCTs) critical care journals (2 RCTs) and a diabetes journal (1 RCT). The topics investigated were

cardiac arrest for 2, septic shock, ARDS, glycemic control, and thromboprophylaxis for the remaining 4.

Details on these 6 RCTs, including survival rates according to randomization arms, are provided in Table 2.

W-WLST reporting

In all the 6 studies, W-WLST were detailed in the results section, either in the plain text (5 RCTs) or in a table (one RCT). W-WLST was addressed in the methods section in one RCT (11). Among those 6, a neurological prognostication pre-specified protocol was detailed in one study, in order to standardize W-WLST decisions by the treating physician (11); two authors answered that no pre-specified protocol was used (12, 13); three did not answer our request (10, 14, 15). Randomized patients underwent a W-WLST decision in 5 RCTs (one article showed no patient with W-WLST). The number of patients with W-WLST decision was detailed by randomization arm in 4, and globally for the whole sample in 1.

Simulation results

Simulation results according to each scenario are presented in Table 3 and Figure 3. Table 3 presents the bias (which should be close to 0) and the coverage probability (*i.e.* the proportion of the time that the 95% confidence interval contains the true value of the hazard ratio, which should close to 0.95) of each analytical method according to the rate of W-WLST decision, the influence of treatment group on W-WLST occurrence, and the effect of treatment group on the overall survival. Figure 3 presents the same data, limited to scenarios with a rate of W-WLST decision of 40% for conciseness.

We will first comment on the performance of the “simple” approach, which compares the overall survival between the two treatment groups without considering the occurrence of W-

WLST decision during the follow-up. In the case of no effect of the treatment group on death and W-WLST decision ($\beta_d = \beta_z = 0$), the “simple” approach provided a correct estimation of the treatment effect and had a coverage close to its nominal value whatever the rate of W-WLST decision. But when β_d differed from 0, a slight bias was observed even in the case of no influence of treatment group on W-WLST decision, with a systematic bias toward zero of the treatment effect estimation, and coverage values slightly below 95%. In the case of non-null β_z , the treatment effect was systematically underestimated with $\beta_z < 0$, and systematically overestimated with $\beta_z > 0$. More precisely, if W-WLST decisions were made less rapidly in the experimental group ($\beta_z < 0$), the experimental group could appear protective despite the absence of real treatment effect ($\beta_d = 0$), less deleterious than reality with $\beta_d > 0$, or more protective than reality with $\beta_d < 0$. These results were more pronounced when the rate of W-WLST decision increased from 20% to 40%.

The “composite” approach had the same issues; with an inflated bias compared to the “simple” approach overall. At the opposite, the “censored” and the “adjusted” approaches had the best performance, with nearly perfect estimation of the treatment effect and correct coverage values in all evaluated scenarios.

DISCUSSION

To the best of our knowledge, this is the very first study looking into how W-WLST are reported in RCTs in critically ill patients and how W-WLST impacts the result on a mortality outcome. This may seem surprising given the fact that W-WLST common in ICU daily clinical practice and frequently followed by death (3–5).

Our first important finding is that W-WLST are scarcely reported in RCTs involved critically ill patients and using a mortality outcome, as they appear only in 6 of 65 (9%) during follow-up.

A W-WLST decision might have direct and rapid consequences on outcome, as death is preceded by W-WLST decisions in almost a half of cases (6,7). To ascertain the importance of W-WLST reporting in clinical trials, we performed a simulation study with different scenarios. We hypothesized that a trial including 1000 subjects had a Day-60 mortality of 50%. The varying parameters were the effect of the randomization arm over the mortality; the effect of the randomization arm on the W-WLST decision; and the rate of W-WLST decision in the population. The simulation study confirmed that a differential timing of W-WLST decisions between the two arms study arms may severely bias the comparison of the mortality outcome. Furthermore, we showed that the intervention could appear protective, if the decision of W-WLST was delayed in the interventional arm, even though the intervention having no effect on survival.

We should highlight that an imbalance between 2 arms in term of such decisions could be the result of: i/ the real effect of the intervention or ii/ a performance bias related to the investigators' belief in the intervention. In the simulation study, we cannot distinguish between these two reasons (real effect or investigators' belief) of imbalance between the 2 arms. However, it is possible to evaluate the robustness of the results against >W-WLST decisions reduce the risk of bias using an "adjusted" or a censored approach. These approaches had the best performance in all evaluated scenarios, allowing passing through the bias of potential unbalance of W-WLST between arms. A large change in the hazard ratio values between the naive (unadjusted) and the adjusted or censored analysis may therefore indicate a performance bias.

The timing from W-WLST decision to death might be short if an organ support is withdrawn. At the contrary, when a decision is to withhold the therapeutic effort, death might occur in a delayed timeline. One may therefore hypothesized that the timing of W-WLST might have a

direct impact on the assessment on the mortality endpoint. Moreover, a performance bias might be presumed if the timing of the decision, from randomization or from the assessment of mortality, is dissimilar between groups, even more if the W-WLST decision is taken just after the evaluation of the mortality endpoint in the intervention group. This eventuality is a huge concern in open-label RCTs.

It is of great interest to underline that, in our review, only one RCT (10) detailed the timing of W-WLST according to randomization arms. It would be useful, when reporting a RCT, to provide not solely the numbers of W-WLST in each arm, their type (withdrawal or withholding of life support), but also to ascertain their proportion and timing, regarding the evaluation of mortality endpoint, is similar between groups. Another way to obviate such bias would be to implement a precise W-WLST protocol for investigators, to standardize this decision. This has been done in only one trial (11), dealing with a situation with a high risk of death (*i.e.* cardiac arrest).

Strengths and limitations

An inherent limitation of a systematic review of published trials is that it may not reflect the features of ongoing RCTs. It therefore seems unlikely that the proportion of W-WLST reporting have changed considerably, especially since no recommendation has been published to promote the use of such reporting in critical care RCTs.

Limitation of the simulation study

The results of the simulation study are limited to a data-generating process focused on only a survival outcome in a limited number of scenarios. Binary outcome (such as death at a specific time point, which is also often used in randomized ICU trials) should also be explored, although there is no reason to think that this type of outcome would be less

influenced by the issues related to W-WLST decision highlighted in this study. If we proposed some simple methods (which can be easily implemented using standard statistical softwares) accounting for the occurrence of W-WLST decision during the follow-up, they should be tested more deeply and compared to other statistical methods such as competing risks or multistate models in this context (16).

Implication for future trials

Since we consider that an imbalance between W-WLST decision could result in a biased result, it seems reasonable to improve the reporting if such decision in RCTs involving critically ill patients. The quality of an RCT depends on the appropriate methodological design and reporting should follow the CONSORT statements in order to provide the readers an unambiguous view of its potential bias and pitfalls. Our proposal is to implement the Consolidated Standards of Reporting Trials (CONSORT) statement with a new recommendation with the objective to improve W-WLST decision reporting in RCT using a mortality outcome (and particularly in case of open-label study).

The ways to improve W-WLST reporting could encompass the four following points. First, a standardized protocol for W-WLST should be established, whenever possible, to homogenize W-WLST decisions in-between randomization groups; second, the rates of W-WLST in each arm should be given, as a result *per se*; third, the timing of W-WLST decision is of utmost importance, as an imbalance in-between randomization arms before or after the assessment of the mortality endpoint would suggest a performance bias; last, a sensitivity analysis accounting for W-WLST decision occurrence during the follow-up could be performed (using the adjusted or the censored approach) to assess the impact of W-WLST decision on the evaluation of the treatment effect, i.e. the robustness of the crude survival analysis.

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Figure 1

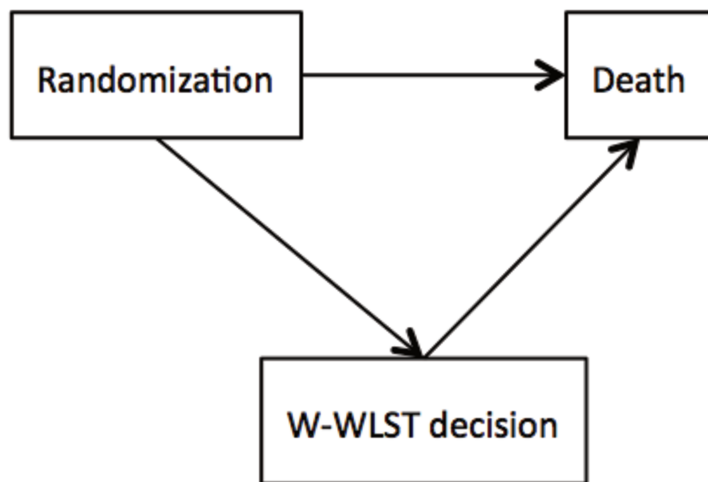


Figure 2: PRISMA Flow diagram.

Among 716 trials identified, 65 reported at least one mortality outcome (as primary or secondary outcome), and were therefore included in this ancillary study.

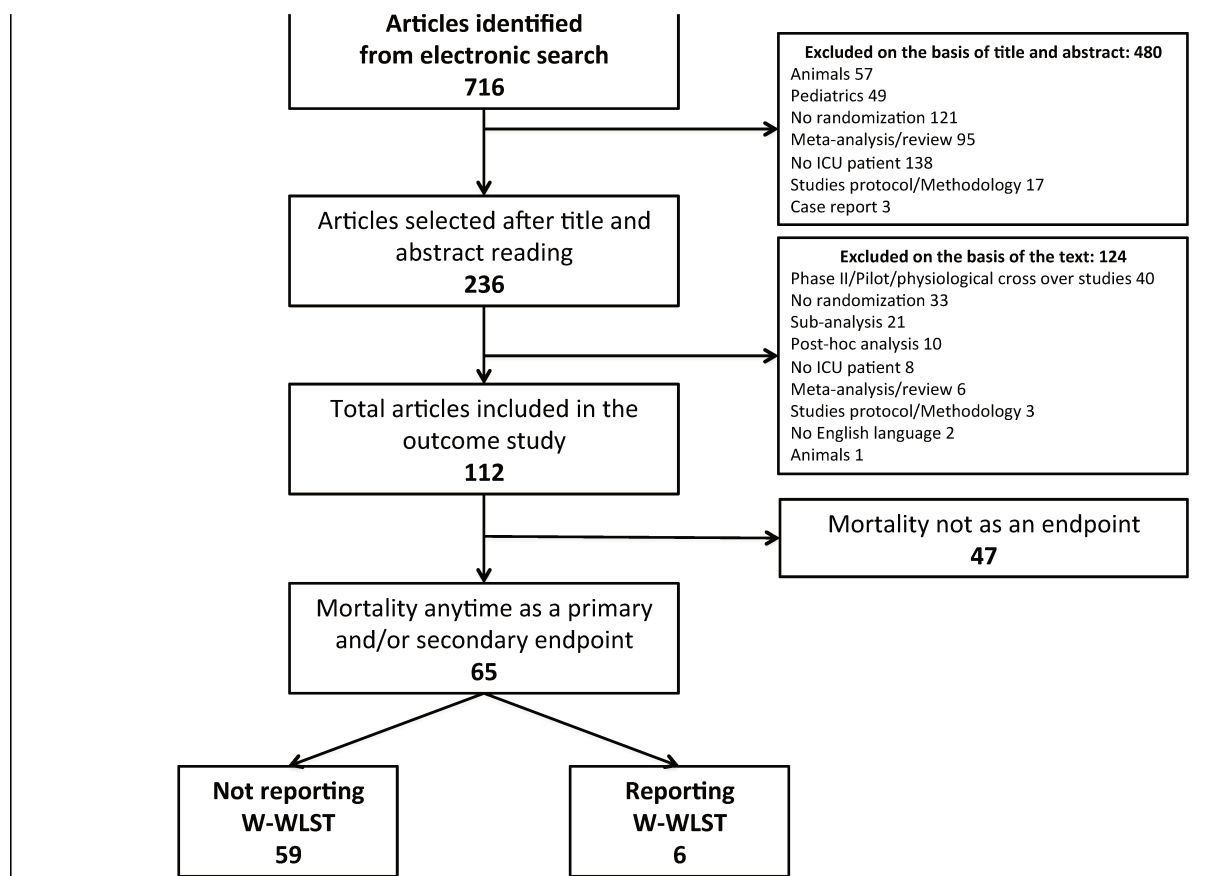


Figure 3: Simulation study, scenarios with a rate of W-WLST decision of 40%

Bias (left) and coverage (right) of each analytical method according to the influence of treatment group on W-WLST occurrence (β_z , i.e. the true log hazard ratio associated with the treatment status on the W-WLST decision), and the true treatment effect on the overall survival (β_d). If β_z differs from $\log(1) = 0$, W-WLST decision occurs more rapidly in the experimental arm ($\beta_z > 0$) or more rapidly in the control arm ($\beta_z < 0$). $\beta_d < 0$ implies protective effect of the experimental arm on survival.

Dotted lines represent either a perfect estimation of the true treatment effect (i.e. bias equal to 0) or a perfect coverage (i.e. coverage equal to 0.95).

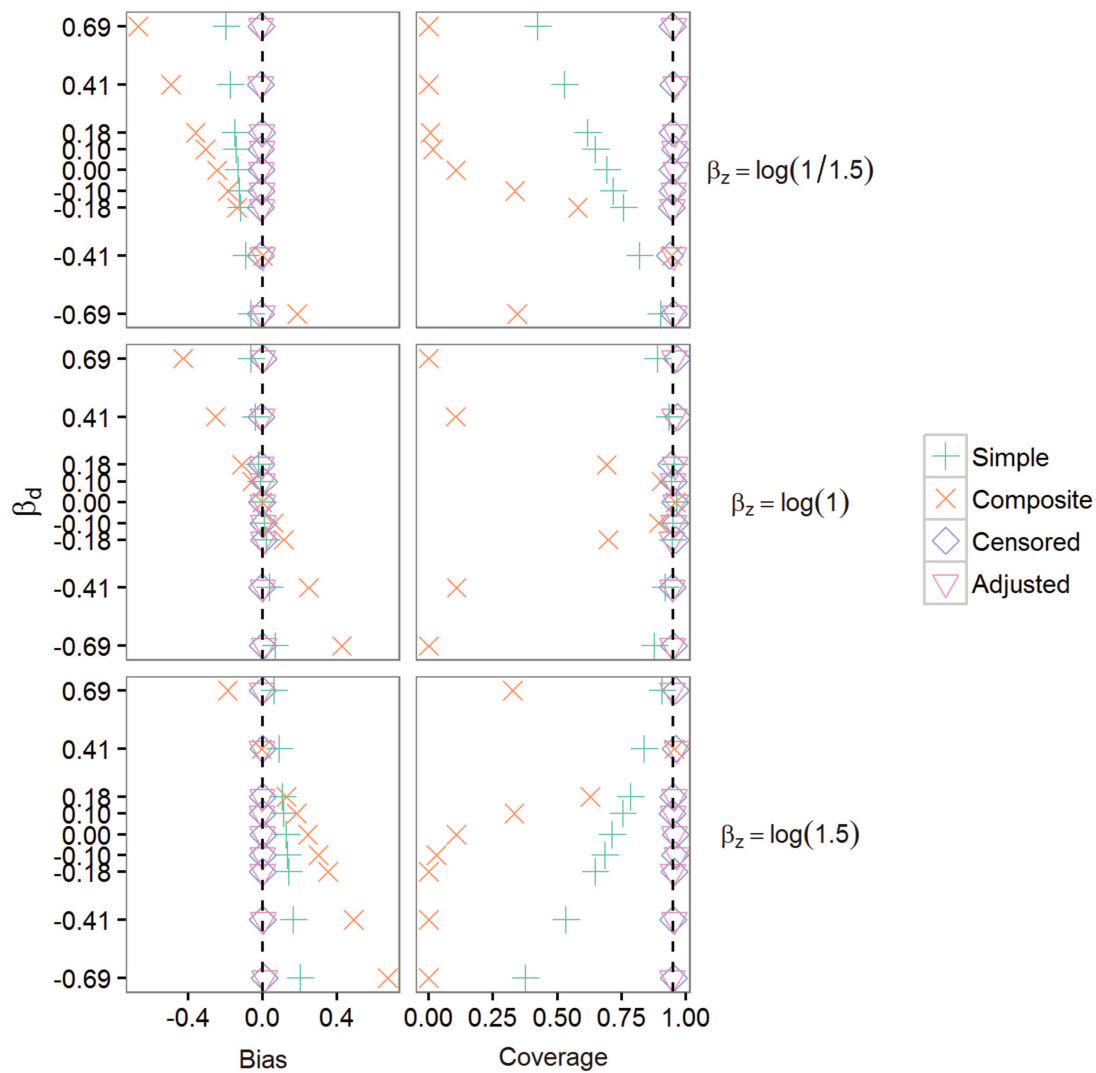


Table 1: Characteristics of the RCTs included in the study. All these RCTs used anytime mortality as a primary and/or secondary outcome.

	All RCTs n=65	RCTs W-WLST not reported n=59	RCTs W-WLST reported n=6
Geographic area*, n (%)			
Europe	32 (49.2)	27 (45.8)	5 (83.3)
Asia	18 (27.7)	17 (28.9)	1 (16.7)
North America	14 (21.5)	13 (22)	1 (16.7)
Oceania	6 (9.2)	5 (8.5)	1 (16.7)
South America	7 (10.7)	6 (10.1)	1 (16.7)
Africa	5 (7.7)	4 (6.8)	1 (16.7)
<i>International (>1 country)</i>	18 (27.7)	16 (27.1)	2 (33.3)
Number of center(s) , n (%)			
Monocenter	28 (43.1)	26 (44.1)	2 (33.3)
Multicenter	35 (53.8)	31 (52.5)	4 (66.7)
Unclear	2 (3.1)	2 (3.4)	
Sample size, n (%)			
<50	12 (18.5)	12 (20.3)	0
50-100	14 (21.5)	13 (22)	1 (16.7)
100-150	5 (7.7)	5 (8.5)	0
150-500	18 (27.7)	15 (25.4)	3 (50)
>500	16 (24.6)	14 (23.7)	2 (33.3)
Topic of the study **, n (%)			
Mechanical ventilation	16 (24.6)	15 (25.4)	1 (16.7)
Sepsis	18 (27.7)	17 (28.8)	1 (16.7)
Nutrition	12 (18.5)	11 (18.6)	1 (16.7)
Infection	10 (15.4)	10 (16.9)	0
Hemodynamics	4 (6.2)	4 (6.8)	0
ARDS	6 (9.2)	5 (8.5)	1 (16.7)
Cardiac arrest	4 (6.2)	2 (3.4)	2 (33.3)
Trauma	2 (3.1)	2 (3.4)	0
Sedation	1 (1.5)	1 (1.7)	0
Acute kidney injury	3 (4.6)	3 (5.1)	0
Pain	2 (3.1)	2 (3.4)	0
Hematological issue	2 (3.1)	2 (3.4)	0
Burns	1 (1.5)	1 (1.7)	0
Extra-corporal membrane oxygenation	1 (1.5)	1 (1.7)	0
Type of intervention, n (%)			
Therapeutic strategy	26 (40)	24 (40.7)	2 (33.3)
Drug	23 (35.3)	20 (33.9)	3 (50)
Device	7 (10.7)	7 (11.9)	0
Monitoring	1 (1.5)	1 (1.7)	0
Diagnostic strategy	4 (6.2)	4 (6.8)	0
Other	4 (6.2)	3 (5.1)	1 (16.7)
Type of trial, n (%)			
Superiority	62 (95.4)	58 (98.3)	4 (66.7)
Equivalence or non-inferiority	3 (4.6)	1 (1.7)	2 (33.3)
Mortality as primary outcome, n (%)	21 (3.2)	17 (28.8)	4 (66.7)
Open-label study, n (%)	40 (61.5)	39 (66.1)	1 (16.7)
ICU survival (%), median [IQR]			
Control arm	68 [54-81]	72 [58-81]	52 [36-93]
Intervention arm	73 [56-84]	74 [57-84]	54 [41-93]

*A single study might appear in more than one row ; ** A single study might have more than one topic

Table 2. Details of the 6 studies in which W-WLST are reported

	Topic of the study	Type of intervention	Type of trial	Survival as an endpoint	Section in which W-WLST are detailed	Comment
Annan et al (15)	Dotrecogin alfa and low dose steroids	Septic shock	Curative, drugs	Superiority	Primary: Day-90 deaths Secondary: Day-28 deaths, at ICU and hospital discharge	Results: in table
Robinson et al (14)	Varying doses of enoxaparin	Thromboprophylaxis	Preventive, drug	Non-inferiority	Secondary: in-hospital mortality	Results: in text All deaths followed W-WLST
Van Herpe et al (10)	Nurse-directed or algorithm-guided glycemic control	Metabolic	Curative, strategy	Non-inferiority	Secondary: in-hospital mortality	Results: in text 7 deaths in the trial
Mentzelopoulos et al (12)	Vasopressin, Steroids and Epinephrine	Cardiac arrest	Curative, drugs	Superiority	Primary: In-hospital deaths	Results: in text
Ferguson et al (13)	High-Frequency Oscillation ventilation	ARDS	Curative, strategy	Superiority	Primary: In-hospital mortality	Results: in text
Nielsen et al (11)	Hypothermia or normothermia	Cardiac arrest	Preventive, strategy	Superiority	Primary: End of the study mortality	In the Methods and Results sections Pre-specified criteria for W-WLST

W-WLST: withholding or withdrawal of life support therapies; ARDS acute respiratory distress syndrome

Table 2: continued

	Number of randomized patients	Male sex (%)	Age (median)	Severity scores	Survival (%)	Number of patients with W-WLST	Number of patients who died after W-WLST
Annan et al (15)	411	65	64	SAPS II 56	At Day-90: Control arm 54 Intervention arm 1 52	35	35
Robinson et al (14)	78	60	60	SAPS II 40.2 APACHE II 20.7	At ICU discharge: Control arm 95 Intervention arm 1 95	4	4
Van Herpe et al (10)	300	62	62	APACHE II 24	At ICU discharge: Control arm 93 Intervention arm 1 92	5	5
Mentzelopoulos et al (12)	300	64	63	n.a.	At Day-60: Control arm 5 Intervention arm 1 14	0	0
Ferguson et al (13)	548	58.4	54	APACHE II 29	At Day-60: Control arm 54 Intervention arm 1 43	118	118
Nielsen et al (11)	939	79	64	n.a.	At 6-month: Control arm 53 Intervention arm 1 52	247	247

W-WLST: withholding or withdrawal of life support therapies; SAPS II: Simplified Acute Physiologic Score II; APACHE II: Acute Physiologic

And Chronic Health Evaluation II; ICU: Intensive Care Unit

Table 3: Results for the estimation of β_d according to the percentage of W-WLST decision β_z , the real treatment effect on risk of death β_d , and the real treatment effect on W-WLST decision β_z . All scenarios had a sample size of $N = 1000$, a censoring rate of $rc = 50\%$, and an effect of the W-WLST status Z on the risk of death of $\delta = \log(4)$.

% ELD	β_z	β_d	Simple		Composite		Censored		Adjusted	
			Bias x 100	Coverage	Bias x 100	Coverage	Bias x 100	Coverage	Bias x 100	Coverage
20%	$\log(1/1.5)$	$\log(1/1.5)$	-4.7	91.9	0.1	94.9	0.0	93.7	0.2	95.4
20%	$\log(1/1.5)$	$\log(1)$	-7.9	86.4	-14.2	59.4	-0.3	95.9	-0.4	95.5
20%	$\log(1/1.5)$	$\log(1.5)$	-10.4	79.1	-28.7	7.1	-0.3	95.3	-0.2	95.3
20%	$\log(1)$	$\log(1/1.5)$	2.8	95.0	14.4	59.6	-0.2	95.3	0.1	95.5
20%	$\log(1)$	$\log(1)$	0.1	94.7	0.1	95.3	0.3	95.6	0.2	94.9
20%	$\log(1)$	$\log(1.5)$	-3.3	93.0	-14.8	56.6	-0.5	95.1	-0.5	95.1
20%	$\log(1.5)$	$\log(1/1.5)$	10.7	77.9	28.6	7.0	0.3	95.1	0.5	94.6
20%	$\log(1.5)$	$\log(1)$	7.1	88.7	13.6	63.6	-0.1	95.0	-0.1	95.2
20%	$\log(1.5)$	$\log(1.5)$	4.9	91.9	0.2	95.2	0.5	94.7	0.0	94.1
40%	$\log(1/1.5)$	$\log(1/1.5)$	-9.0	82.1	0.3	94.5	-1.0	93.7	0.2	95.1
40%	$\log(1/1.5)$	$\log(1)$	-13.2	69.2	-24.3	10.7	-0.7	94.6	-0.7	95.9
40%	$\log(1/1.5)$	$\log(1.5)$	-17.1	52.8	-49.2	0.0	-0.8	94.9	-1.0	95.9
40%	$\log(1)$	$\log(1/1.5)$	3.8	91.9	24.9	10.9	-0.1	94.7	0.2	94.8
40%	$\log(1)$	$\log(1)$	0.0	96.5	-0.2	96.0	-0.3	95.8	0.0	96.0
40%	$\log(1)$	$\log(1.5)$	-3.8	93.4	-25.3	10.5	-0.5	96.8	-0.1	95.4
40%	$\log(1.5)$	$\log(1/1.5)$	16.7	53.4	49.0	0.0	0.1	94.9	0.4	95.5
40%	$\log(1.5)$	$\log(1)$	12.7	71.3	24.4	10.8	0.4	95.9	0.0	95.4
40%	$\log(1.5)$	$\log(1.5)$	8.9	83.8	-0.5	95.4	0.2	95.9	-0.3	96.5

4/ ESSAI CONTROLE RANDOMISE AKIKI

4-1 Justification de l'étude

Nous avons mené un essai contrôlé randomisé sur les critères d'initiation de l'épuration extrarénale en réanimation chez des patients souffrant d'insuffisance rénale aigue sévère. Ce travail a fait l'objet d'un financement au Programme Hospitalier de Recherche Clinique National 2012 (AOM12456).

L'insuffisance rénale aiguë est une situation fréquente chez les patients de réanimation qui est associée à une morbidité et une mortalité importantes (69–72). Malgré de nombreuses études sur les modalités d'épuration extrarénale (7, 32, 73, 74), il n'existait jusqu'à présent que peu de données de qualité sur les critères d'initiation de l'épuration extra-rénale en dehors bien entendu des situations de danger vital immédiat (hyperkaliémie menaçante, acidose métabolique profonde et oedème pulmonaire liée à la surcharge générant une hypoxémie profonde). La recherche clinique sur les critères d'initiation de l'épuration extra-rénale en réanimation est d'ailleurs considérée comme une priorité (75). Les études de cohorte existantes ne permettent pas de répondre à cette question car elles comparent le délai d'initiation (précoce ou tardive) de l'épuration extra-rénale chez des patients qui sont par définition systématiquement épurés (76). Or l'intérêt d'une stratégie tardive d'épuration extra-rénale est d'éviter d'exposer un certain nombre de patients aux risques de l'épuration extrarénale en attendant que leur fonction rénale récupère (77). Ainsi, pour répondre à cette question avec le plus haut niveau de preuve, nous avons comparé des stratégies d'initiation d'épuration extra-rénale précoce et tardive en randomisant les patients à un stade défini de gravité d'insuffisance rénale aiguë.

4-2 Choix des critères de jugement

Compte tenu de la gravité des patients inclus dans cette étude, la mortalité attendue était d'approximativement 50%. Il nous a donc semblé justifié d'utiliser la mortalité comme critère de jugement principal, ce qui est un *patient-important outcome*.

Par ailleurs, les décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives étant particulièrement fréquentes dans cette population de patients très graves (mortalité attendue de 50%), nous les avons rapportées en tant que critère de jugement secondaire.

4-3 Objectif de l'étude

Le protocole de l'essai AKIKI (Artificial Kidney Initiation in Kidney Injury) (78) a été écrit dans l'objectif de comparer 2 stratégies d'initiation de l'épuration extra-rénale chez des patients atteints d'insuffisance rénale aiguë sévère (stade 3 de la classification de KDIGO (79)) :

- Une stratégie d'initiation précoce où les patients étaient épurés dans les 6 heures suivant l'apparition des critères d'inclusion
- Une stratégie d'attente où les patients n'étaient épurés qu'en présence d'au moins un des 5 critères prédéfinis (hyperkaliémie menaçante, acidose métabolique ou mixte profonde, oedème pulmonaire de surcharge générant une hypoxémie importante, taux d'urée plasmatique > 40 mmol/l et durée de l'oligo-anurie > 3 jours).

4-4 Méthodologie

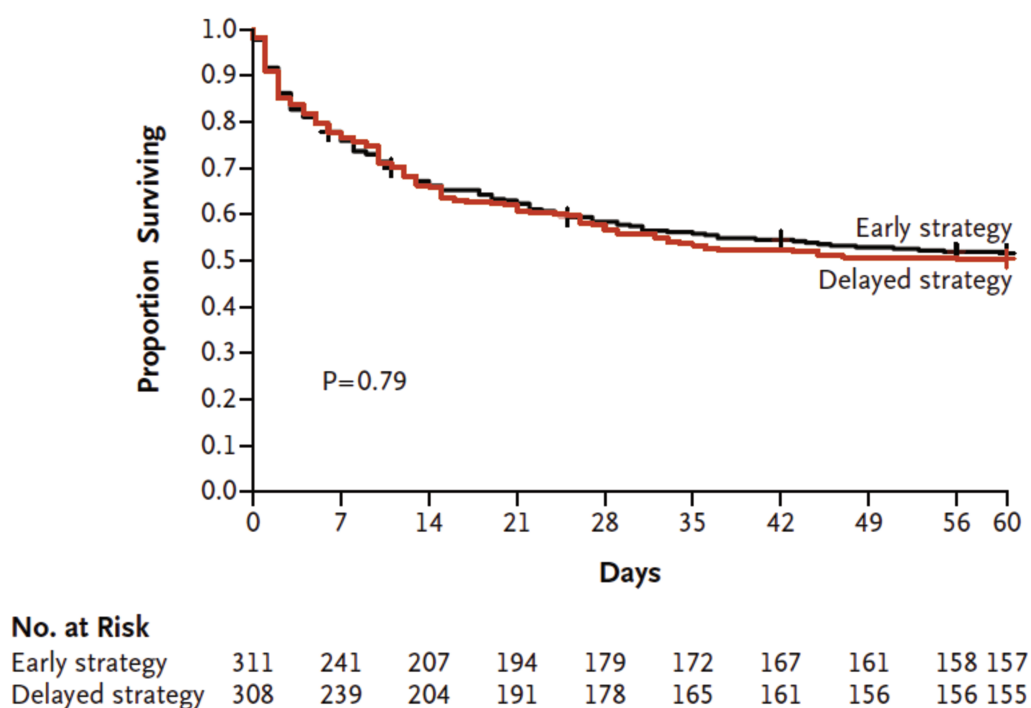
Cet essai contrôlé randomisé ouvert multicentrique s'est déroulé entre septembre 2013 et janvier 2016. Les patients sous ventilation mécanique ou nécessitant la perfusion de catécholamines et présentant une insuffisance rénale aiguë sévère (stade 3 de la classification de KDIGO (79)) étaient randomisés en 2 bras : une stratégie précoce d'épuration extrarénale et une stratégie

d'attente. Dans la stratégie précoce, le patient était épuré immédiatement après la randomisation. Dans la stratégie d'attente, le patient était épuré uniquement si un des critères suivants apparaissaient : hyperkaliémie sévère, acidose métabolique profonde, œdème pulmonaire de surcharge générant une hypoxémie profonde, urée > 40mmol/l ou oligo-anurie > 72 heures. Le critère de jugement était la survie globale 60 jours après la randomisation. Le taux de décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives faisait partie des critères de jugement secondaires.

4-5 Résultats principaux

La stratégie d'attente a permis d'éviter le recours à l'épuration extra-rénale chez près de la moitié des patients sans qu'une différence de mortalité ne soit observée 60 jours après la randomisation (Figure 5).

Figure 5 : Probabilité de survie des patients dans l'étude AKIKI (de la randomisation à J60)



Nous n'avons pas observé de différence entre le bras « stratégie précoce » et le bras « stratégie d'attente » en terme de taux de décision de limitations thérapeutiques (71/311 (23%) et 73/308

(24%) respectivement, $p=0,78$) ou de délai de prise de ces décisions par rapport à la randomisation (6 [2-12] et 8 [3-14] jours respectivement, $p=0,23$).

4-6 Article 3: Comparison of 2 strategies for initiating renal replacement therapy in the intensive care unit: study protocol for a randomized controlled trial (AKIKI) (Trials 2015; 16:170)

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STUDY PROTOCOL

Open Access

Comparison of two strategies for initiating renal replacement therapy in the intensive care unit: study protocol for a randomized controlled trial (AKIKI)

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Abstract

Background: There is currently no validated strategy for the timing of renal replacement therapy (RRT) for acute kidney injury (AKI) in the intensive care unit (ICU) when short-term life-threatening metabolic abnormalities are absent. No adequately powered prospective randomized study has addressed this issue to date. As a result, significant practice heterogeneity exists and may expose patients to either unnecessary hazardous procedures or undue delay in RRT.

Methods/design: This is a multicenter, prospective, randomized, open-label parallel-group clinical trial that compares the effect of two RRT initiation strategies on overall survival of critically ill patients receiving intravenous catecholamines or invasive mechanical ventilation and presenting with AKI classification stage 3 (KDIGO 2012). In the 'early' strategy, RRT is initiated immediately. In the 'delayed' strategy, clinical and metabolic conditions are closely monitored and RRT is initiated only when one or more events (severity criteria) occur, including: oliguria or anuria for more than 72 hours after randomization, serum urea concentration >40 mmol/l, serum potassium concentration >6 mmol/l, serum potassium concentration >5.5 mmol/l persisting despite medical treatment, arterial blood pH <7.15 in a context of pure metabolic acidosis ($\text{PaCO}_2 < 35$ mmHg) or in a context of mixed acidosis with a $\text{PaCO}_2 \geq 50$ mmHg without possibility of increasing alveolar ventilation, acute pulmonary edema due to fluid overload despite diuretic therapy leading to severe hypoxemia requiring oxygen flow rate >5 l/min to maintain $\text{SpO}_2 > 95\%$ or $\text{FiO}_2 > 50\%$ under invasive or noninvasive mechanical ventilation.

The primary outcome measure is overall survival, measured from randomization (D0) until death, regardless of the cause. The minimum follow-up duration for each patient will be 60 days. Two interim analyses are planned, blinded to group allocation. It is expected that there will be 620 subjects in all.

(Continued on next page)

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Discussion: The AKIKI study will be one of the very few large randomized controlled trials evaluating mortality according to the timing of RRT in critically ill patients with AKI classification stage 3 (KDIGO 2012). Results should help clinicians decide when to initiate RRT.

Trial registration: ClinicalTrials.gov NCT01932190.

Keywords: Acute kidney injury, Critical care, Renal replacement therapy, Treatment outcome

Background

Acute kidney injury (AKI) is common in intensive care unit (ICU) patients [1-3]. Despite progress in symptomatic management of AKI and technical advances in renal replacement therapy (RRT) techniques [4], mortality remains very high (50 to 60%) [5].

Life-threatening metabolic complications, such as severe hyperkalemia or overload pulmonary edema responsible for refractory hypoxemia, are accepted indications for RRT during AKI [6,7]. In contrast, the accumulation of uremic or other putative toxins has not been shown to be a risk factor *per se* for mortality in AKI and cannot be used as a reliable indication for RRT. Similarly, severe gastrointestinal bleeding, a classical complication of AKI, has almost disappeared during AKI for multiple reasons (better management of infection and shock, prophylaxis with inhibitors of gastric acid secretion) [8,9].

Although many authors and experts favor early RRT [10-12], some hypothesized that too early an RRT initiation might be harmful [13,14]. Several studies have recently suggested that delaying or even avoiding RRT could benefit patients with AKI [15,16]. These uncertainties result in significant practice heterogeneity [17], making a randomized controlled trial on the timing of RRT initiation not only ethically justified but also desired by many clinicians.

To the best of our knowledge, only one such large randomized controlled study is ongoing [18], while another is due to start in the near future [19].

The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial is a multicenter randomized controlled trial comparing the effects of an 'early' RRT initiation strategy with a 'delayed' strategy on overall survival of critically ill patients (invasive mechanical ventilation or catecholamine infusion).

Methods/design

Design and settings

The AKIKI study is a prospective, multicenter, open-label, two-arm randomized study. This study is conducted of patients receiving invasive mechanical ventilation or catecholamine infusion who have AKI classification stage 3 (KDIGO 2012) [20]. An 'early' strategy where RRT is initiated immediately after randomization will be compared

with a 'delayed' strategy, where RRT is initiated only if one or more 'severity' (potentially life-threatening complications of AKI) criteria occur. These criteria are:

- Oliguria or anuria for more than 72 hours after randomization,
- Serum urea concentration >40 mmol/l,
- Serum potassium concentration >6 mmol/l,
- Serum potassium concentration >5.5 mmol/l persisting despite medical treatment (bicarbonate or glucose-insulin infusion),
- pH <7.15 in a context of pure metabolic acidosis ($\text{PaCO}_2 < 35$ mmHg) or in a context of mixed acidosis with $\text{PaCO}_2 \geq 50$ mmHg without possibility of increasing alveolar ventilation,
- Acute pulmonary edema due to fluid overload leading to severe hypoxemia requiring oxygen flow rate >5 l/min to maintain $\text{SpO}_2 > 95\%$ or $\text{FiO}_2 > 50\%$ in patients already undergoing invasive or noninvasive mechanical ventilation and despite diuretic therapy.

Patients have to be adequately resuscitated (fluid and or catecholamine infusion) before potential inclusion; this is to avoid enrolling patients with rapidly reversible renal failure and to allow clinician to diagnose acute tubular necrosis with reasonable accuracy.

Ethical aspects

The study protocol and information forms were approved by the ethical committee of the French Society of Intensive Care Medicine (Société de Réanimation de Langue Française, approval number CE SRLF 13-005) and by the competent French legal authority (*Comité de Protection des Personnes d'Ile de France VI, Groupe Hospitalier Pitié Salpêtrière*; registration number: 2013-A00765-40; date of approval 29 May 2013).

Patients are informed orally and provided with a written document about the AKIKI study by the investigators. By French law, written informed consent is not required, as the standard of care encompasses both study interventions. As already mentioned, patients or surrogates are informed about the trial and their right to refuse participation. If the patient is unable to receive

appropriate information, decision is made by a substitute decision maker. Patients who are eligible but incapable of receiving information and for whom a substitute decision maker is not available may be randomized through a process of deferred information. They are informed about participation as soon as their clinical status allows.

Participating intensive care units

A total of 31 French ICUs are participating in the study. All study sites have medical and paramedical teams who are experienced in the field of RRT. Because data in the literature fail to suggest a conclusion on a definite benefit of one RRT modality over another (intermittent hemodialysis or continuous techniques), the choice of RRT modality is left to the team's discretion depending on their usual practice. In each study site, RRT prescription and monitoring are standardized according to the French national guidelines from panel experts [21].

Study population

Eligible patients are adults (≥ 18 years) hospitalized in study ICUs with AKI compatible with the diagnosis of acute tubular necrosis in a context of ischemic or toxic aggression and receiving invasive mechanical ventilation or catecholamine infusion. To be randomized, patients must fulfill at least one of the three following criteria: serum creatinine concentration $> 354 \mu\text{mol/l}$ or greater than three times the baseline creatinine level, anuria (urine output $< 100 \text{ ml}$) for more than 12 hours, oliguria (urine output $< 0.3 \text{ ml/kg/h}$ or $< 500 \text{ ml/day}$) for more than 24 hours. These three criteria represent stage 3 of the KDIGO classification [20].

Patients presenting with one of the accepted indications for immediate RRT (severity criteria) at baseline assessment are not included

Other non-inclusion criteria are pre-existing severe chronic renal failure (defined by creatinine clearance $< 30 \text{ ml/min}$); patients already included in the study; patients with inclusion criteria already present for more than 5 hours (to avoid delayed inclusions); AKI caused by urinary tract obstruction, renal vessel obstruction, tumor lysis syndrome, thrombotic microangiopathy, or acute glomerulopathy; poisoning by a dialyzable agent; Child C liver cirrhosis; cardiac arrest without awakening; moribund state (patient likely to die within 24 h); patient having already received RRT for the current episode of AKI; extracorporeal lung or circulatory assistance; patients included in another clinical study of a RRT technique.

All patients treated with invasive mechanical ventilation or catecholamine infusion with AKI of a lesser degree than stage 3 of KDIGO classification are screened for eligibility by the physicians and clinical research nurses around the

clock and 7 days a week. Reasons for non-inclusion of all eligible patients are collected.

Randomization

Eligible patients are consecutively randomly allocated to one of the two study treatment arms, termed 'early' and 'delayed' RRT strategies. Randomization and concealment are achieved using a centralized, secure, computer-generated, interactive, web-response system accessible from each study center. The randomization is balanced by blocks of variable and undisclosed size and stratified on the center. Before randomization, the presence of the inclusion criteria and the absence of the non-inclusion criteria are verified. The randomization day is the study day zero (D0).

Study interventions

The study protocol and both arms of randomization are detailed in Figure 1.

When indicated (allocation to early RRT strategy or occurrence of at least one severity criterion in patients allocated to delayed RRT strategy), RRT is initiated as quickly as possible.

As already explained, the choice of RRT modality is left to the study site's discretion. Several RRT modalities can be used in the same patient, according to the attending physician's indication. The duration of and interval between sessions, and device settings and modality of anticoagulation are left to the investigator's discretion.

Clinical and biological parameters are monitored, to detect and treat any complication directly (hyperkalemia, metabolic acidosis, pulmonary edema) or indirectly (bleeding, infection, thrombosis...) related to AKI or RRT.

'Early' RRT strategy

Renal replacement therapy is initiated within 6 hours after documentation of AKI stage 3 of KDIGO classification. The timing of the initiation is recorded and RRT is continued until criteria for cessation are observed.

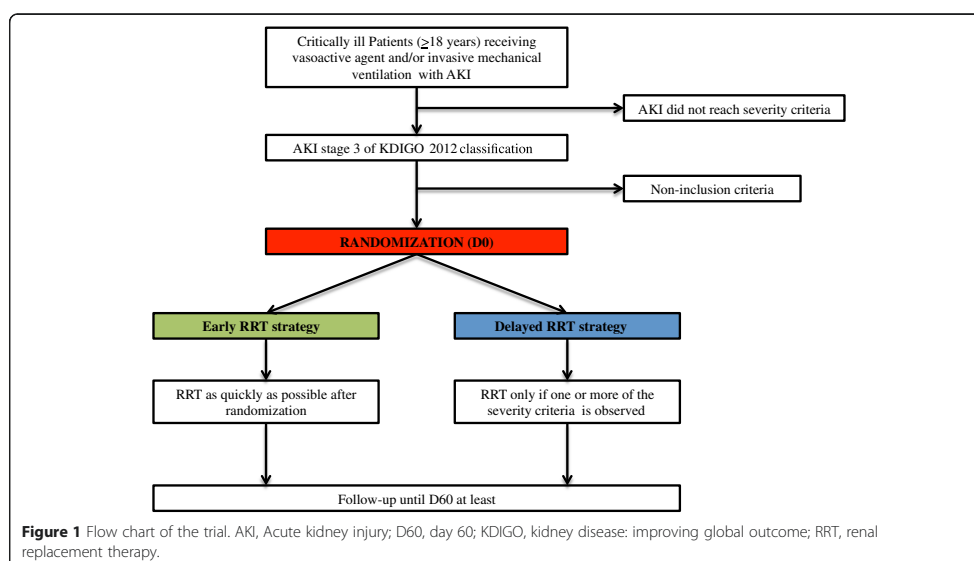
'Delayed' RRT strategy

Renal replacement therapy is initiated only if one or more of the severity criteria occur. When required, RRT is performed with the same modalities and stopped according to the same criteria as for the 'early' RRT strategy.

Criteria for RRT cessation

Discontinuation of RRT is contemplated if spontaneous diuresis is $\geq 500 \text{ ml}$ per 24 h, and highly recommended if diuresis is $> 1000 \text{ ml}$ per 24 h without diuretic administration or $\geq 2000 \text{ ml/24 h}$ in patients receiving diuretics.

Cessation of RRT is mandatory if diuresis is present and serum creatinine level decreases spontaneously.



Criteria for RRT resumption

In the absence of sufficient renal function recovery to achieve a spontaneous decrease in creatinine level or of a diuresis greater than 1000 ml/24 h without diuretics (or greater than 2000 ml/24 h under diuretics), RRT is resumed.

Authorized treatments (whatever the arm randomization)

Pharmacological prevention of gastrointestinal bleeding

Given the risk factors for digestive bleeding in this population (mechanical ventilation or catecholamine infusion in patients with severe AKI), and in the absence of consensus on this issue in available guidelines, the protocol recommends the use of a proton pump inhibitor.

Use of diuretics

Diuretics should only be used for the treatment of obvious sodium and fluid overload in patients whose diuresis is ≤ 500 ml per 24 h.

Use of sodium polystyrene sulfonate and isotonic sodium bicarbonate administration will be left to the clinician's discretion.

Fluid therapy, including red blood cell transfusion, is left to the investigator's discretion.

The use of hydroxyethyl starch solutions is discouraged.

Data collection and follow-up

At day zero (D0)

Demographic data and medical history, including the current clinical history with the reason for ICU admission,

Simplified Acute Physiology Score III and Sequential Organ Failure Assessment score will be collected. Potential exposure to nephrotoxic agents (for example, aminoglycosides or contrast agents) will be documented. Details of treatments including mechanical ventilation (and its settings), fluid therapy, catecholamine and anticoagulant administration are recorded.

Laboratory tests include determination of serum (and urine if diuresis is present) electrolyte levels, serum glucose level, urea and creatinine concentration, arterial blood gas content, and liver and muscle enzyme concentrations. No renal failure marker identification (such as neutrophil gelatinase-associated lipocalin) is planned because the clinical usefulness of these markers in routine care has not yet been demonstrated [19].

Baseline (that is, before occurrence of AKI) serum creatinine concentration will be recorded. Baseline serum creatinine concentration will be determined from either the results of a measurement in the 12 months preceding the ICU stay or estimated using the Modification of Diet in Renal Disease Study Group formula [22]. As a special case, if serum creatinine concentration was measured more than 12 months before admission, the baseline level will be considered as the higher of the two estimates (former serum concentration or that computed using the Modification of Diet in Renal Disease formula).

From D1 to D28

The same biological data as collected at inclusion will be recorded according to clinical indication for routine care

until discharge from the ICU, day 28 in the ICU, or death in the ICU. A search for infection (including catheter-related infection) or complications related to RRT or AKI will be carried out according to routine care procedures. The Sequential Organ Failure Assessment score will also be calculated at D3, D7, D14, D21, and D28.

At D60

Vital status (alive or dead) and duration of hospital and ICU stay will be recorded. Details and timings of patient follow-up are summarized in Table 1.

After D60

Vital status and dialysis dependency will regularly be updated for each patient until the end of the study (that is, day 60 after inclusion of the last patient).

Organization of the trial

Funding and support

The AKIKI trial is promoted by the Assistance Publique - Hôpitaux de Paris and supported by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2012; AOM12456).

Table 1 Flowchart of patient follow-up

	D0 inclusion	Daily from D1 to D28	D28	D60
Inclusion and exclusion criteria	X			
Demographic data and history	X			
Clinical assessment	X	X		
Laboratory tests	X	X		
Baseline creatininemia	X			
Simplified Acute Physiology Score III	X			
Sequential Organ Failure Assessment	X	D3, D7, D14, D21, D28		
Mechanical ventilation	X	X		
Treatment with catecholamines	X	X		
Renal replacement therapy initiation	X	X		
Renal replacement therapy technique used	X	X		
Complications of renal replacement therapy or acute kidney injury		X		
Total cost of renal replacement therapy				X
Duration of stay in intensive care unit or hospital			X	X
Alive or dead status			X	X

Coordination and implementation of the trial

Each medical and paramedical team in the 31 participating ICUs were trained in the protocol and data collection using an electronic case-record form during formal meetings prior to screening and inclusion. The electronic case-record form was developed with CleanWEB™, a centralized, secure, interactive, web-response system accessible from each study center, provided and managed by Telemedicine Technologies.

Local physicians and clinical research assistants in each participating ICU are responsible for daily screening and inclusion of patients, compliance with protocol, availability of data requested for the trial and completion of the electronic case-record form. In accordance with French law, the electronic case-record form and database were validated by appropriate committees (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé; Commission Nationale de l'Informatique et des Libertés).

Interim analysis

Two interim analyses by an independent data safety and monitoring board are planned after the occurrence of 90 and 180 deaths. The data safety and monitoring board will be blinded to allocation of groups and may decide premature termination of the study. The board consists of one methodologist, one nephrologist, and two intensivists. Data are blindly analyzed but unblinding is possible on request of the data safety and monitoring board. An extraordinary meeting may be requested by the principal investigator or the methodologist, in the case of unexpected events that might affect continuation of the protocol.

Blinding

Given the nature of the interventions, physicians, nurses, and patients cannot be blinded for the randomized interventions. Lack of blinding is, however, partially counterbalanced by the objective nature of the primary outcome measure [23]. The analysis will be blinded to allocation of groups.

Study outcomes

Primary endpoint

The primary endpoint measure is the overall survival. Overall survival is measured from the randomization date (D0) until death, regardless of the cause. For patients discharged alive, information on the primary endpoint measure will be collected by a telephone call to the patient's home or by a conversation with the physician in charge, if the patient is still in a care facility. The minimum follow-up duration for each patient will be 60 days. The status (alive or dead) of patients lost to follow-up before the planned follow-up duration will be checked by obtaining their birth

certificate (eventual demise is indicated in this official document) from the City Hall of their city of birth (French law allows anyone to ask for such certificate). Patients for whom vital status remains unknown at D60 (a rare occurrence) or who are still alive at the end of their follow-up period will be censored at the last date to which their health status has been documented.

Secondary endpoints

Secondary endpoint measures are the percentage of patients receiving RRT at least once in the 'delayed' RRT strategy arm (compared with the 100% of patients in the 'early' strategy); the number of RRT sessions per patient (analyzing living and dead patients separately); the time between randomization (D0) and RRT initiation; the time between observation of at least one of the severity criteria (which mandates RRT in the delayed strategy) and RRT; the time to RRT weaning; the number of days alive without RRT (between D0 and up to D28); the time between D0 and the first RRT and between the last RRT and D60; the number of dialysis catheter-free days between D0 and D28; the rate of adverse events potentially related to AKI or RRT (including: (a) hemorrhage requiring red blood cell transfusion or surgical procedure, (b) thrombocytopenia ($<100,000$ platelets/mm³), (c) thrombosis of a large venous axis diagnosed by Doppler ultrasonography, (d) hypokalemia (defined as serum potassium concentration <3 mmol/l), (e) hypophosphatemia (defined as a serum phosphate concentration <0.6 mmol/l), (f) hyperkalemia (>6.5 mmol/l), (g) cardiac rhythm disorders (ventricular tachycardia, ventricular fibrillation, torsades de pointes or a new episode of atrial fibrillation requiring medical treatment or external electric counter shock); the number of days alive without mechanical ventilation between D0 and D28; the rate of nosocomial infections (bloodstream, lung and catheters and unexplained bacteremia or fungemia); the number of days alive without vasopressors between D0 and D28; the progression of organ failures assessed using the Sequential Organ Failure Assessment score; the duration of stay in the ICU and in hospital generally (limited to D60); the survival rate at D28; the proportion of patients with treatment limitations (withholding or withdrawal); and the total cost of RRT-related consumables between D0 and D28 (catheters, solutions for RRT, membranes, and circuitry).

Statistical methods

Sample size calculation

The aim of this study is to demonstrate a difference in outcome between two therapeutic strategies. Our primary hypothesis is that the 'delayed' RRT strategy might be beneficial to patients with AKI. The sample size calculation is based on the primary endpoint measure: overall survival.

The expected mortality of patients included in this type of studies may be estimated at around 55%, according to the literature [2,24–26]. Indirect evidence from retrospective studies [13,16] suggests that a 15% decrease in mortality can be expected with delayed indication for RRT (the reasons for this are explained in the discussion section).

To demonstrate a 14% decrease in mortality (from 55 to 41%, corresponding to a relative reduction in the risk of mortality by 1.5 in the 'delayed' RRT strategy arm, assuming exponential survival), a total of 546 subjects (273 per group) should be randomized to provide a study power of 90%, with an alpha risk of 5% between both treatments (bilateral formulation).

Interim analyses

Two blind and independent interim analyses (making a total of three analyses) are planned in this study. Interim analyses will be conducted after the observation of 90 and 180 deaths.

To maintain an overall type I error rate of 5%, the significance level of each analysis is adjusted, using the O'Brien & Fleming approach of group sequential analysis [27]. To maintain a power of 90%, this approach provides an increase in the planned number of subjects required for a single analysis; that is, 560 subjects instead of 546. Table 2 describes the number of events required for each analysis, the planned number of subjects and the significance levels applied for testing (with due correction).

Total planned sample size

To take into account a potential loss to follow-up of about 10%, it is expected that a total of 620 subjects will be enrolled in this study.

Methodology of the statistical analysis

A patient follow-up chart will describe the number of eligible patients and the number of patients actually included (total and per arm).

For each group and at each assessment date, qualitative variables will be described as number and percentage, and quantitative variables as number, mean, and standard

Table 2 Number of deaths, expected number of subjects, and significance level of testing at each preplanned analysis of the primary outcome

	Number of deaths	Expected number of subjects	Significance level α
Single analysis	263	546	5%
Interim analyses:			
First analysis	90	187	0.15%
Second analysis	180	373	1.81%
Final analysis	270	560*	4.37%

*To take into account a potential loss to follow-up of about 10%, it is planned to include a total of 620 subjects in the study.

deviation. Quantitative variables with skewed distribution will be presented as median and interquartile range (25th percentile to 75th percentile).

Analysis of the primary endpoint

The overall survival (primary endpoint), estimated using the Kaplan-Meier method, will be analyzed in the intention-to-treat population.

Regarding the comparison of the survival between the 'early' and 'delayed' arms, the assumptions are: H0: Relative risk (RR) = 1 and H1: RR $\neq$ 1. This comparison will be based on the log-rank test.

For the first and second interim analyses, this test will be performed at an alpha risk of 0.15% and 1.81%, respectively. If the test is significant, the null hypothesis will be rejected and it will be concluded that there is a difference in overall survival between strategies. The inclusion of patients in the study will then be terminated early.

If the inclusion has not been terminated after the two planned interim analyses, the final analysis will be performed when 620 patients will be included, after the 60 days of follow-up of the last included patient. This analysis will be performed at an alpha risk of 4.37%.

All these tests will be performed with a bilateral formulation.

Other analyses

Categorical variables will be compared using the χ^2 or Fisher's test, as appropriate. Continuous variables will be compared using Student's *t* test or the Wilcoxon test, as appropriate.

The analysis of the overall survival will be adjusted for important stratification and prognostic factors using a multivariate analysis (Cox model). The adjustment factors will include: baseline Simplified Acute Physiology Score III, RRT technique used, treatment with catecholamines at baseline, mechanical ventilation at baseline, septic shock at baseline, time between admission in ICU and AKI development (less than, greater than, or equal to 7 days).

All secondary analyses will be conducted at the bilateral alpha risk of 5%.

Analyses will be performed using R software (R Foundation for Statistical Computing, Vienna, Austria) version 2.14 or later, or SAS version 9.2.

Discussion

When to start RRT is one of the key questions during severe AKI in critically ill patients. Recent expert panel opinions considered that answering this question is one of the top priorities in research on AKI [7].

Life-threatening hyperkalemia, acute overload pulmonary edema generating severe hypoxemia, and uremic complications (pericarditis and encephalopathy) are the

only indisputable emergency RRT criteria [6,7]. Apart from these situations, there is considerable debate on the potential merits of an early RRT strategy, which would allow better immediate control of metabolic disorders but expose patients to potential adverse effects, in particular complications associated with catheter and extracorporeal circulation and of a delayed strategy that would minimize these risks at the price of more severe or prolonged metabolic disorders.

Indeed, placing an unstable patient with septic shock (or other circulatory compromise) on RRT is not devoid of risk, even in experienced teams [28]. By the same view, delaying RRT for several hours or even days may allow RRT to be initiated in a stabilized patient and, in the best case scenario, may allow spontaneous recovery of renal function, avoiding unnecessary RRT. However, such an approach entails increased risk of metabolic or unknown complications.

To the best of our knowledge, apart from this study, only two prospective randomized studies are actually addressing [18] or plan to address this issue [19], with mortality as the main endpoint measure. Both studies share the premise that early RRT would be better than late. In contrast, the AKIKI study is the only one that tests a completely opposite hypothesis.

All three studies seem to share similar criteria for early initiation: RRT is started in the few hours following observation of severe AKI in patients who are adequately resuscitated to discard the hypothesis of rapidly reversible renal failure.

Unlike the two other studies, we think that the risk associated with early RRT may exceed that related to delayed RRT. Our hypothesis of a reduction of mortality with a delayed strategy is based on an analysis of the literature that shows that patients with the so-called usual criteria for RRT (but without obvious life-threatening electrolyte or fluid-balance abnormality) may have an excellent prognosis, with mortality rates between 26 and 31% [15,16].

We hypothesize that patients in the delayed RRT strategy arm may have a chance of recovering acceptable renal function, obviating the need for RRT and that the others may have RRT performed in better conditions.

Trial status

Enrollment is ongoing, having started on September 2013. The first interim analysis was conducted in August 2014, and the data safety and monitoring board recommended that the study be continued. On December 14, 2014, 322 patients were included in the trial. Enrollment is expected to be completed in March 2016.

Abbreviations

AKI: Acute kidney injury; AKIKI: Artificial Kidney Initiation in Kidney Injury; DO: Day zero; ICU: Intensive care unit; RRT: Renal replacement therapy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SG, DD, and DH drafted the manuscript. SG, DD, DH, FS, LM-L, J-DR, and FT participated in the design of the AKIKI study and contributed to revisions of the original manuscript. DH and FT performed the statistical plan and sample size calculation. SG, FS, LM-L, BP, EB, AB (Alexandre Boyer), NL, GC, DC, AL, AB (Anne Bretagnol), JM, MT, PM, GT, JD, JR, MD, NdP, HY, BM, YL, CB, JM, BZ, SN, NB, IH, J-DR, and DD are involved in acquisition of data. All authors edited the manuscript and read and approved the final manuscript.

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4-7 Article 4: Initiation strategy for renal replacement therapy in intensive care unit (NEJM 2016; 375:122-133)

Stéphane Gaudry, David Hajage, Frédérique Schortgen, Laurent Martin-Lefevre, Bertrand Pons, Eric Boulet, Alexandre Boyer, Guillaume Chevrel, Nicolas Lerolle, Dorothée Carpentier, Nicolas de Prost, Alexandre Lautrette, Anne Bretagnol, Julien Mayaux, Saad Nseir, Bruno Megarbane, Marina Thirion, Jean-Marie Forel, Julien Maizel, Hodane Yonis, Philippe Markowicz, Guillaume Thiery, Florence Tubach, Jean-Damien Ricard, Didier Dreyfuss, for the AKIKI study group

ORIGINAL ARTICLE

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

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ABSTRACT

BACKGROUND

The timing of renal-replacement therapy in critically ill patients who have acute kidney injury but no potentially life-threatening complication directly related to renal failure is a subject of debate.

METHODS

In this multicenter randomized trial, we assigned patients with severe acute kidney injury (Kidney Disease: Improving Global Outcomes [KDIGO] classification, stage 3 [stages range from 1 to 3, with higher stages indicating more severe kidney injury]) who required mechanical ventilation, catecholamine infusion, or both and did not have a potentially life-threatening complication directly related to renal failure to either an early or a delayed strategy of renal-replacement therapy. With the early strategy, renal-replacement therapy was started immediately after randomization. With the delayed strategy, renal-replacement therapy was initiated if at least one of the following criteria was met: severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen level higher than 112 mg per deciliter, or oliguria for more than 72 hours after randomization. The primary outcome was overall survival at day 60.

RESULTS

A total of 620 patients underwent randomization. The Kaplan–Meier estimates of mortality at day 60 did not differ significantly between the early and delayed strategies; 150 deaths occurred among 311 patients in the early-strategy group (48.5%; 95% confidence interval [CI], 42.6 to 53.8), and 153 deaths occurred among 308 patients in the delayed-strategy group (49.7%, 95% CI, 43.8 to 55.0; $P=0.79$). A total of 151 patients (49%) in the delayed-strategy group did not receive renal-replacement therapy. The rate of catheter-related bloodstream infections was higher in the early-strategy group than in the delayed-strategy group (10% vs. 5%, $P=0.03$). Diuresis, a marker of improved kidney function, occurred earlier in the delayed-strategy group ($P<0.001$).

CONCLUSIONS

In a trial involving critically ill patients with severe acute kidney injury, we found no significant difference with regard to mortality between an early and a delayed strategy for the initiation of renal-replacement therapy. A delayed strategy averted the need for renal-replacement therapy in an appreciable number of patients. (Funded by the French Ministry of Health; ClinicalTrials.gov number, NCT01932190.)

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*A complete list of investigators in the Artificial Kidney Initiation in Kidney Injury (AKIKI) Study Group is provided in the Supplementary Appendix, available at [nejm.org](http://www.nejm.org).

Drs. Hajage and Schortgen contributed equally to this article.

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ACUTE KIDNEY INJURY IS A COMMON condition among patients in the intensive care unit¹⁻⁴ and is associated with high morbidity and mortality.^{2,5-8} Renal-replacement therapy is the cornerstone of the management of severe acute kidney injury. Many studies have focused on methods of renal-replacement therapy,^{5,6,8,9} but the issue of when to initiate the therapy in the absence of a potentially life-threatening complication directly related to renal failure remains a subject of debate. Indirect evidence has suggested that early renal-replacement therapy could confer a survival benefit.¹⁰⁻¹² However, two observational studies reported high survival rates among patients who did not receive renal-replacement therapy,^{13,14} and one study reported adverse outcomes in association with very early renal-replacement therapy in patients with sepsis.¹⁵ Early initiation of renal-replacement therapy may allow for better control of fluid and electrolyte status, removal of uremic toxins, and prevention of complications such as gastric hemorrhage and metabolic encephalopathy.¹⁶ Delaying renal-replacement therapy initiation is intuitively unlikely to have any immediate benefit per se. However, a delay may allow time for the stabilization of a patient's condition before renal-replacement therapy is initiated and may avoid the need for such support, which is not devoid of risk.¹⁷

Given such uncertainties, there is heterogeneity among criteria for the initiation of renal-replacement therapy.^{18,19} Indeed, several authorities consider an appropriate multicenter, randomized, controlled trial involving patients with acute kidney injury to be an important research priority.^{20,21} To fill this perceived need, in the current trial we compared a strategy of early initiation of renal-replacement therapy with a strategy of delayed initiation in patients in the intensive care unit who had acute kidney injury of Kidney Disease: Improving Global Outcomes (KDIGO) classification stage 3 (serum creatinine, 3.0 times the baseline level or ≥ 4.0 mg per deciliter [≥ 354 μmol per liter]; urine output, <0.3 ml per kilogram of body weight per hour for 24 or more hours or anuria for ≥ 12 hours).²²

METHODS

TRIAL DESIGN AND OVERSIGHT

The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial was an institutionally sponsored,

unblinded, prospective, multicenter, open-label, two-group randomized trial conducted in 31 intensive care units in France from September 2013 through January 2016. The protocol (which has been published previously²³) was approved by the ethics committee of the French Society of Intensive Care Medicine and by the appropriate French legal authority (Comité de Protection des Personnes d'Ile de France VI) for all participating centers and is available with the full text of this article at NEJM.org. The Direction de la Recherche Clinique de l'Assistance Publique-Hôpitaux de Paris, French Ministry of Health, supervised the use of the study funding.

The investigators informed patients or their surrogates about the trial both orally and with a written document. In accordance with French law, written informed consent was not required, because the standard of care encompasses both study interventions. Patients or their surrogates were informed that they could decline to participate at any time, and their decision was recorded in patient files (see the Supplementary Appendix, available at NEJM.org).

The trial was overseen by a steering committee that presented information regarding the rate of inclusion of new patients to the investigators by e-mail every 3 months and during meetings in January 2014 and January 2015. Two planned interim analyses were performed by an independent data and safety monitoring board, the members of which were unaware of the study-group assignments. An investigator at each center was responsible for enrolling patients, ensuring adherence to the protocol, and completing the electronic case-report form. The first author vouches for the accuracy and the completeness of the reported data and for the adherence of the trial to the protocol. All analyses were performed by the study statistician (the second author) in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines.

PATIENTS

Patients were eligible if they were adults (18 years of age or older) who were admitted to the intensive care unit with acute kidney injury that was compatible with a diagnosis of acute tubular necrosis in the context of ischemic or toxic injury and were receiving invasive mechanical ventilation, catecholamine infusion (epinephrine or norepinephrine), or both. To undergo randomization,

patients were required to have KDIGO stage 3 acute kidney injury (see the Supplementary Appendix).²² The main exclusion criteria at the time of enrollment were the following severe laboratory abnormalities: a blood urea nitrogen level higher than 112 mg per deciliter (40 mmol per liter), a serum potassium concentration greater than 6 mmol per liter (or greater than 5.5 mmol per liter despite medical treatment), a pH below 7.15 in the context of either pure metabolic acidosis (partial pressure of arterial carbon dioxide [P_{aCO_2}] below 35 mm Hg) or mixed acidosis (P_{aCO_2} of 50 mm Hg or more without the possibility of increasing alveolar ventilation), and acute pulmonary edema due to fluid overload responsible for severe hypoxemia requiring an oxygen flow rate greater than 5 liters per minute to maintain a peripheral capillary oxygen saturation (SpO_2) greater than 95% or requiring a fraction of inspired oxygen (FiO_2) greater than 50% in patients receiving mechanical ventilation and despite diuretic therapy. These criteria were later used to establish the indication for renal-replacement therapy in patients assigned to the delayed strategy (i.e., therapy was initiated in that group if any of these laboratory abnormalities developed after enrollment). Other exclusion criteria are detailed in the Supplementary Appendix.

RANDOMIZATION

The randomization list was computer-generated, balanced by blocks of variable and undisclosed size, and stratified according to center. Patients underwent randomization within 5 hours after validation of stage 3 acute kidney injury (which left 1 hour to initiate renal-replacement therapy in patients who were assigned to the early strategy); patients were randomly assigned in a 1:1 ratio to either early initiation of renal-replacement therapy (early-strategy group) or delayed initiation of renal-replacement therapy (delayed-strategy group). Concealment of the study-group assignments was achieved with the use of a centralized, secure, interactive, Web-based response system (CleanWeb, Telemedicine Technologies) that was accessible from each study center.

INTERVENTIONS

In the early-strategy group, renal-replacement therapy was initiated as soon as possible after randomization in order for it to be started within 6 hours after documentation of stage 3 acute kidney in-

jury. In the delayed-strategy group, renal-replacement therapy was initiated if one of the laboratory abnormalities defined above developed or if oliguria or anuria lasted for more than 72 hours after randomization (Table S1 in the Supplementary Appendix). The choice of the method of renal-replacement therapy (intermittent or continuous technique, duration and interval between sessions, device setting, and anticoagulation method) was left to the discretion of each study site and was prescribed and monitored according to national guidelines.²⁴ All centers had extensive experience in both the management of acute kidney injury and techniques of renal-replacement therapy.

In both groups, discontinuation of renal-replacement therapy was considered if the spontaneous urine output was 500 ml or higher per 24 hours and was highly recommended if the spontaneous urine output was higher than 1000 ml per 24 hours in the absence of diuretic therapy or if urine output was higher than 2000 ml per 24 hours in patients who were receiving diuretic therapy. Discontinuation of renal-replacement therapy was mandatory if diuresis was sufficient to allow for spontaneous decrease in serum creatinine concentration. Renal-replacement therapy was resumed if diuresis appeared to be insufficient to result in a spontaneous decrease in creatinine level or if urine output fell below 1000 ml per 24 hours in the absence of diuretic therapy (or below 2000 ml per 24 hours in patients receiving diuretic therapy).

OUTCOMES

The duration of follow-up for each patient was 60 days from randomization. The primary outcome was overall survival measured from the date of randomization until death or day 60. For patients who were discharged alive from the intensive care unit, information on the primary outcome was obtained either directly from the patient or the patient's relatives or from the physician who was in charge when the patient was still hospitalized. Data from patients who were alive at day 60 were censored, and data from patients who were lost to follow-up before day 60 were censored at their last follow-up assessment.

The secondary outcomes were the receipt of renal-replacement therapy at least once with the delayed strategy; the numbers of renal-replacement therapy-free days, dialysis catheter-free days, mechanical ventilation-free days, and vasopressor

therapy-free days (i.e., days alive and without the intervention; a value of 0 days was assigned for patients who died) between randomization and day 28; the Sepsis-related Organ Failure Assessment (SOFA) score²⁵ at day 3 and day 7; the vital status at day 28; the length of stay in the intensive care unit and in the hospital; the proportion of patients with treatment limitations (i.e., withholding or withdrawal of treatment); the occurrence of nosocomial infections; and complications potentially related to acute kidney injury or renal-replacement therapy (see the Supplementary Appendix).

Other prespecified outcomes included the time between randomization and the initiation of renal-replacement therapy, the time between the occurrence of at least one of the criteria that mandated renal-replacement therapy in the delayed-strategy group and actual initiation of therapy, the number of sessions of renal-replacement therapy, and dependence on renal-replacement therapy at days 28 and 60. Because diuresis was closely monitored, we also noted the number of patients who, for at least 1 day, had urine output of more than 1000 ml per 24 hours in the absence of diuretic therapy or of more than 2000 ml per 24 hours with diuretic therapy and who did not require initiation or resumption of renal-replacement therapy for at least 7 days. The total numbers of units of red cells transfused was also compared. These outcomes had not been prespecified in the protocol when the trial was being designed.

STATISTICAL ANALYSIS

This trial was designed as a sequential study (with two interim analyses)²⁶ (see the Supplementary Appendix). On the basis of published data, death at day 60 was expected in 55%^{6,7,9,27} of patients requiring renal-replacement therapy in the intensive care unit. At the time that the trial was being designed, indirect evidence^{13,14,28} suggested that mortality might be expected to be 15 percentage points lower in association with delayed renal-replacement therapy. We calculated that with a total sample size of 546 patients, the study would have 90% power to show a 15-percentage-point lower mortality with the delayed strategy than with the early strategy (corresponding to a relative risk of 0.65 in favor of the delayed strategy, under an assumption of an exponential distribution of survival times), at a two-sided alpha level of 5%. Two interim effi-

cacy analyses were planned, after the observation of 90 and 180 deaths. To maintain an overall type I error rate of 5%, the significance level of each analysis was adjusted with the use of the O'Brien and Fleming approach.²⁹ To maintain a power of 90%, this approach also necessitated an increase in the planned number of patients, to 560. To take into account a potential loss to follow-up of 10%, enrollment of 620 patients was planned.

Baseline characteristics in each study group were analyzed as frequencies and percentages for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables, as appropriate. The overall survival (primary outcome), estimated by the Kaplan–Meier method, was analyzed in the intention-to-treat population and compared between the two groups with the use of a log-rank test. Further stratification according to center, adjustment for baseline prognostic factors (Simplified Acute Physiology Score [SAPS] III, treatment or no treatment with vasopressors, receipt or no receipt of mechanical ventilation, presence or absence of septic shock, and time between admission to the intensive care unit and development of acute kidney injury of <7 days vs. ≥7 days), and determination of baseline predictors of renal-replacement therapy in the delayed-strategy group were also performed with a Cox semiparametric proportional-hazards model.

Categorical variables were compared with the use of the chi-square test or Fisher's exact test, and continuous variables were compared with the use of Student's *t*-test or Wilcoxon test, as appropriate. The time to recovery of renal function, as marked by diuresis, was described by means of the Kaplan–Meier method and compared with a log-rank test. For this analysis, data from all patients were censored at the time of death or at day 28.

With the exception of the primary outcome (for which the type I error rate was adapted for interim analyses), all analyses were performed at a two-sided alpha level of 5%. All analyses were performed with R software, version 3.2.3 (R Foundation for Statistical Computing).

RESULTS

PATIENTS

A total of 5528 patients were eligible for inclusion in the trial, and 620 patients underwent random-

ization (Fig. S1 in the Supplementary Appendix); 312 were assigned to the early-strategy group and 308 were assigned to the delayed-strategy group. One patient in the early-strategy group subsequently withdrew consent for the use of his data, leaving a total of 619 patients in the analysis.

The characteristics of the patients were well balanced between the two study groups, with the exception of the prothrombin ratio (i.e., the ratio of a patient's prothrombin time to that in a control sample, expressed as a percentage), which was significantly lower in the delayed-strategy group (Table 1, and Table S2 in the Supplementary Appendix). Sepsis was present in 494 patients (80%), and 389 patients (63%) had been exposed to nephrotoxic agents.

RENAL-REPLACEMENT THERAPY

The patients in the early-strategy group underwent their first renal-replacement therapy session within a median of 2 hours (interquartile range, 1 to 3) after randomization and within a median of 4.3 hours (interquartile range, 2.7 to 5.9) after documentation of stage 3 acute kidney injury and of the fulfillment of other inclusion criteria. In this group, six patients did not receive renal-replacement therapy (see the Supplementary Appendix).

A total of 157 patients (51%) received renal-replacement therapy in the delayed-strategy group within a median of 57 hours (interquartile range, 25 to 83) after randomization (Fig. 1). The median interval between the occurrence of at least one criterion mandating renal-replacement therapy and its initiation was 4.7 hours (interquartile range, 1.7 to 10.0). Five patients received renal-replacement therapy without meeting the initiation criteria. Persistence of oliguria or anuria for more than 72 hours after randomization and a blood urea nitrogen level higher than 112 mg per deciliter (40 mmol per liter) were the two most common reasons for renal-replacement therapy (Table S3 in the Supplementary Appendix).

Patient characteristics at the time of initiation of renal-replacement therapy are provided in Table S4 in the Supplementary Appendix. Metabolic abnormalities were more marked in the delayed-strategy group than in the early-strategy group. Details regarding the methods used for renal-replacement therapy, the changes in blood urea nitrogen and serum creatinine levels during follow-up, and the baseline predictors of renal-

replacement therapy in the delayed-strategy group are provided in the Supplementary Appendix.

PRIMARY AND SECONDARY OUTCOMES

Follow-up data at 60 days were available for 614 patients (99%); a total of 303 deaths had been observed by day 60 (150 in the early-strategy group and 153 in the delayed-strategy group). The mortality rates in our analysis were estimated with the use of the Kaplan–Meier method. The Kaplan–Meier estimate of the overall mortality at day 60 was 49.1% (95% confidence interval [CI], 45.0 to 52.9). Mortality did not differ significantly between the two study groups: 48.5% (95% CI, 42.6 to 53.8) in the early-strategy group and 49.7% (95% CI, 43.8 to 55.0) in the delayed-strategy group ($P=0.79$) (Fig. 1). Further stratification according to center and adjustment for important prognostic factors did not materially change the results.

A post hoc exploratory analysis was performed to compare patients who never received renal-replacement therapy with those who received it either early or late. The lowest mortality at day 60 (37.1%) was found among patients who never received renal-replacement therapy, and the highest mortality (61.8%) was found among patients who received therapy late, whereas intermediate mortality (48.5%) was found among patients who received therapy early ($P<0.001$). Patients who never received renal-replacement therapy were less ill at baseline, and patients who received it late were the most severely ill patients at baseline. The differences in mortality became nonsignificant after adjustment for baseline severity of illness, which suggests that these observed differences were markedly confounded (see the Supplementary Appendix).

In the delayed-strategy group, 95 patients (61%) of the 155 who were alive at day 60 had not received renal-replacement therapy, and the total number of therapy sessions differed substantially between the study groups (Table S5 in the Supplementary Appendix). Mortality at day 28, numbers of mechanical ventilation-free and vasopressor-free days, length of stay in intensive care unit and in the hospital, and dependence on renal-replacement therapy at day 28 and 60 did not differ significantly between the two study groups (Table 2). However, the number of days free from renal-replacement therapy was significantly higher, and the rate of catheter-related

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Early Strategy (N=311)	Delayed Strategy (N=308)
Age — yr	64.8±14.2	67.4±13.4
Serum creatinine before ICU admission — mg/dl†	0.95±0.26	0.97±0.31
Coexisting conditions — no. (%)		
Chronic renal failure	22 (7)	38 (12)
Hypertension	161 (52)	167 (54)
Diabetes mellitus	82 (26)	81 (26)
Congestive heart failure	24 (8)	32 (10)
Ischemic heart disease	30 (10)	32 (10)
SAPS III at enrollment‡	72.6±14.4	73.7±14.2
SOFA score at enrollment§	10.9±3.2	10.8±3.1
Exposure to at least one nephrotoxic agent in past 2 days — no./total no. (%)¶	194/311 (62)	195/308 (63)
Intravenous contrast	66/194 (34)	71/195 (36)
Aminoglycoside	106/194 (55)	106/195 (54)
Vancomycin	26/194 (13)	29/195 (15)
Physiological support — no. (%)		
Invasive mechanical ventilation	266 (86)	267 (87)
Vasopressor support with epinephrine or norepinephrine	265 (85)	263 (85)
Sepsis status — no. (%)		
Sepsis	25 (8)	21 (7)
Severe sepsis	16 (5)	19 (6)
Septic shock	209 (67)	204 (66)
Patients with oliguria or anuria — no. (%)	202 (65)	191 (62)
Serum creatinine — mg/dl	3.25±1.40	3.20±1.32
Blood urea nitrogen — mg/dl	53±24	54±24
Serum potassium — mmol/liter	4.4±0.7	4.4±0.7
Serum bicarbonate — mmol/liter	18.7±5.1	18.8±5.5

* Plus-minus values are means ±SD. A total of 620 patients underwent randomization, and 1 patient subsequently withdrew permission for the use of his data. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for blood urea nitrogen to millimoles per liter, multiply by 0.357. Additional data on baseline characteristics are provided in Table S2 in the Supplementary Appendix. ARDS denotes acute respiratory distress syndrome, and ICU intensive care unit.

† The serum creatinine concentration before ICU admission was either determined with the use of values measured in the 12 months preceding the ICU stay or was estimated.²²

‡ The Simplified Acute Physiology Score (SAPS) III ranges from 0 to 146, with higher scores indicating more severe disease and a higher risk of death.

§ The Sepsis-related Organ Failure Assessment (SOFA) score ranges from 0 to 24, with higher scores indicating more severe organ failure.²⁵

¶ Some patients were exposed to more than one nephrotoxic agent.

|| Sepsis was defined as suspected or confirmed infection, with at least two of four signs of a systemic inflammatory response. Severe sepsis was defined as sepsis with evidence of organ dysfunction. Septic shock was defined as sepsis-induced hypotension despite fluid resuscitation of at least 30 ml per kilogram of body weight of intravenous fluid administered within the period spanning the 4 hours before and 4 hours after initiation of vasopressor therapy.

bloodstream infections was significantly lower, in the delayed-strategy group than in the early-strategy group (Table 2).

The rate of complications that were poten-

tially related to acute kidney injury or renal-replacement therapy did not differ significantly between the two study groups, with the exception of hypophosphatemia, which was more

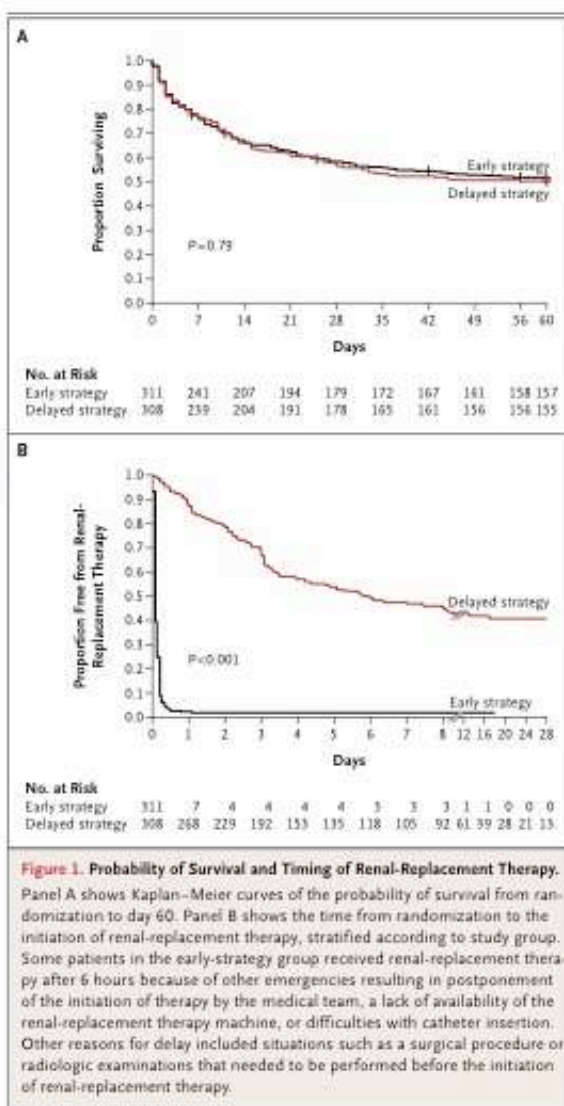
common in the early-strategy group (Table 2). The overall rate of hemorrhage did not differ significantly between the study groups (Table 2). Whereas there was no significant difference between the groups in the rate of either dialysis catheter-related or digestive-tract blood loss, blood loss from other causes was significantly more common in the delayed-strategy group (Table S8 in the Supplementary Appendix). The numbers of patients who received red cells and the amount of red cells received per patient did not differ significantly between the groups (Table 2). Adequate diuresis together with no need for renal-replacement therapy were observed earlier in the delayed-strategy group than in the early-strategy group ($P<0.001$) (Fig. 2).

DISCUSSION

In this trial, a strategy of delayed initiation of renal-replacement therapy in critically ill patients with severe acute kidney injury obviated the need for renal-replacement therapy in almost 50% of cases (resulting in a considerable difference in the total number of renal-replacement therapy sessions). Mortality at day 60 did not differ significantly between the early-strategy group and the delayed-strategy group.

The available knowledge about the initiation of renal-replacement therapy during acute kidney injury derives predominantly from observational studies.^{31–33} Meta-analyses have suggested that a survival advantage is associated with early renal-replacement therapy.^{34,35} A major pitfall of such observational studies is that all patients received renal-replacement therapy — that is, there was no control group, and the possibility that delaying renal-replacement therapy might provide time for spontaneous renal recovery was not explored. Two small, single-center, randomized, controlled trials have addressed this issue,^{27,36} but they showed no difference in mortality. The current results address the timing of renal-replacement therapy.²⁵ Two other large multicenter studies are in progress,^{37,38} and we speculate that the results of those studies will confirm our findings, particularly because a pilot study showed that a delayed strategy averted the need for renal-replacement therapy in an appreciable number of patients.³⁹

The 50% mortality among patients in our trial was close to our working hypothesis and conso-



nant with the rate in other studies.^{37–4} Patients in the current study received renal-replacement therapy at a median of 2 hours after randomization with the early strategy and at a median of 57 hours with the delayed strategy. Contrary to our hypothesis, no survival benefit was observed with the delayed strategy of renal-replacement therapy.

Table 2. Primary and Secondary Outcomes and Adverse Events.*

Outcome	Early Strategy (N = 311)	Delayed Strategy (N = 308)	P Value	Hazard Ratio (95% CI)
Death — no. (% [95% CI])†				
Day 28	129 (41.6 [35.9–46.9])	134 (43.5 [37.7–48.8])		
Day 60	150 (48.5 [42.6–53.8])	153 (49.7 [43.8–55.0])	0.79	1.03 (0.82–1.29)
Adjusted analysis‡			0.84	1.02 (0.81–1.29)
Patients with treatment limitation in ICU — no. (%)§	71 (23)	73 (24)	0.78	
Median study day on which a treatment limitation first occurred (IQR)¶	6 (2–12.5)	8 (3–14)	0.23	
Patients who received renal-replacement therapy — no. (%)	305 (98)	157 (51)	<0.001	
Median renal-replacement therapy–free days (IQR)	17 (2–26)	19 (5–29)	<0.001	
Median mechanical ventilation–free days (IQR)	7 (0–22)	6 (0–21)	0.76	
Median vasopressor-free days (IQR)	20 (1–26)	20 (0–26)	0.67	
SOFA score				
Day 3	10±4	10±4	0.14	
Day 7	8±4	8±4	0.63	
SOFA score without renal component				
Day 3	8±4	8±4	0.62	
Day 7	6±4	6±3	0.94	
Median length of ICU stay (IQR)				
Survivors	13 (8–23)	13 (7–23)	0.87	
Nonsurvivors	6 (2–14)	6 (2–13)	0.92	
Median length of hospital stay (IQR)				
Survivors	29 (17–51)	32 (20–51)	0.58	
Nonsurvivors	6 (2–14)	6 (2–13)	0.85	
Nosocomial infection				
Catheter-related bloodstream infection				
Patients with infection — no. (%)¶¶	31 (10)	16 (5)	0.03	
Median incidence per 1000 catheter-days (IQR)	3.4 (2.3–4.6)	2.1 (1.1–3.1)	0.09	
Unexplained bloodstream infection — no. (%)	21 (7)	26 (8)	0.43	
Ventilator-associated pneumonia — no. (%)	50 (16)	37 (12)	0.15	

Complications potentially related to acute kidney injury or renal-replacement therapy — no. (%)			
Hemorrhage	27 (9)	36 (12)	0.21
Thrombocytopenia	172 (55)	165 (54)	0.70
Thrombosis	11 (4)	16 (5)	0.31
Hypokalemia	69 (22)	67 (22)	0.95
Hypophosphatemia	69 (22)	46 (15)	0.03
Hyperkalemia	16 (5)	18 (6)	0.68
Cardiac rhythm disorders — no. (%)			
Severe	29 (9)	35 (11)	0.40
Moderate	49 (16)	48 (16)	0.77
Transfusion			
Patients who received transfusion — no. (%)	146 (47)	152 (49)	0.57
Units of red cells transfused per patient	2.4±4.1	2.4±4.3	0.75
Dependence on renal-replacement therapy — no./total no. (%)			
Day 28	22/179 (12)	17/178 (10)	0.51
Day 60	3/157 (2)	8/155 (5)	0.12

* Plus-minus values are means ±SD. The numbers of days free from renal-replacement therapy, mechanical ventilation, and vasopressor therapy was defined as the number of days alive without the intervention at day 28; for patients who died, a value of 0 days was assigned. IQR denotes interquartile range.

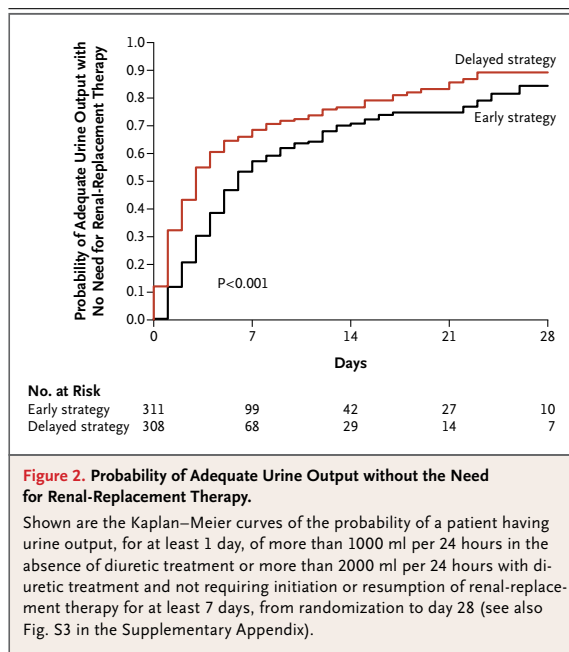
† Mortality rates were estimated with the use of the Kaplan–Meier method. The vital status at day 60 was not available for 7 patients (see the Supplementary Appendix).

‡ This analysis was stratified according to center and adjusted for the following baseline characteristics: receipt or no receipt of mechanical ventilation, SAPS III, presence or absence of septic shock, treatment or no treatment with vasopressors, and time between admission and acute kidney injury.

§ Treatment limitations (withholding or withdrawal of treatment) could involve any treatment used during the ICU stay.

¶ Catheter-related bloodstream infections were defined according to the 2009 guidelines from the Infectious Diseases Society of America.³⁰

|| Definitions are provided in the Supplementary Appendix.



Although the survival curves were similar in the two groups, the recovery of renal function, as marked by diuresis, was more rapid and catheter-related infections occurred less frequently in the delayed-strategy group than in the early-strategy group. Subtle or undetected circulatory alterations might have slowed the apparent recovery of renal function in the early-strategy group. The rate of gastrointestinal bleeding did not differ significantly between the groups. Finally, the lengths of stay in the intensive care unit and in the hospital were similar in the two groups, which indicates that allowing time for renal function recovery did not lead to prolongation of the stay in the intensive care unit.

Our findings may not be generalizable, because more than 50% of the patients in our trial received intermittent hemodialysis as the first method of therapy and only 30% of the patients received continuous renal-replacement therapy as the sole method (with no intermittent dialysis at any time). Although a previously published large, randomized, controlled trial did not show differences in mortality according to the method of renal-replacement therapy,⁹ some investigators

have voiced concern about the potentially deleterious effects of intermittent hemodialysis in patients whose condition is unstable.⁴⁰

Our trial has potential limitations. First, the power of our study to distinguish a significant difference in mortality could be questioned. However, to detect an effect size of 1.2 percentage points (i.e., the difference in mortality that we found between the two groups in our study) with a power of 90%, a sample of more than 70,000 patients would be required. Second, although we did not use Kt/V (a measure of the clearance of urea in which K represents the rate of urea clearance by the dialyzer, t is the duration of dialysis, and V is the volume of distribution of urea in the patient) to evaluate the dose of renal-replacement therapy, low urea levels in serum were maintained during therapy. Third, the patients in the trial population had advanced acute kidney injury, and therefore our results may not be generalizable to patients with different KDIGO stages of acute kidney injury. Finally, some could interpret the finding of higher mortality among patients who received late renal-replacement therapy as a deleterious effect of this strategy. However, the patients who received late renal-replacement therapy obviously had more severe illness than those who did not, and further adjustment according to baseline severity suggests that this observed crude difference was confounded (see the Supplementary Appendix).

Our study should not be interpreted as suggesting that a “wait and see” approach is safe for all patients. Indeed, careful surveillance is mandatory when deciding to delay renal-replacement therapy in patients with severe acute kidney injury so that any complication will be detected and renal-replacement therapy initiated without delay. In our trial, delaying the initiation of therapy allowed many patients to recover from acute kidney injury without embarking on such a treatment course.

In conclusion, our trial involving critically ill patients with severe acute kidney injury showed no significant difference in mortality with a strategy of delayed initiation as compared with early initiation of renal-replacement therapy.

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APPENDIX

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5/ SYNTHESE

Nos travaux ont porté sur deux points spécifiques concernant les critères de jugement dans les essais contrôlés randomisés en réanimation.

En se plaçant dans la perspective du patient, nous sommes partis du constat que les décisions thérapeutiques des cliniciens réanimateurs avaient 2 objectifs essentiels : sauver la vie des patients et limiter au mieux les conséquences physiques et/ou psychiques de la réanimation ayant un impact sur la qualité de vie des patients. Nous avons évalué dans quelle proportion les essais cliniques randomisés en réanimation utilisaient des critères de jugement en lien avec ces objectifs. Nous avons ainsi défini des *patient-important outcomes* spécifiques à ces patients. Une limite de ce travail réside dans l'absence de participation des patients à la définition des *patient-important outcomes* adaptée à la réanimation. En effet, nous avons construit cette définition à partir de notre situation de témoins de ce que vivent les patients en réanimation et après leur hospitalisation (dans notre service de réanimation médico-chirurgicale, nous effectuons occasionnellement des consultations de suivi à 3 mois, 6 mois et 1 an de la sortie des patients dans le cadre d'un protocole de recherche clinique (Etude SUIVIREA, identifiant clinicaltrial: NCT01796509)). La participation d'un groupe de patient à la construction de cette définition aurait pu aboutir à une définition différente.

Ce premier travail a montré qu'une faible proportion d'essais contrôlés randomisés en réanimation utilisait un *patient-important outcome* comme critère de jugement principal et que cela n'avait pas évolué récemment. Par ailleurs, la plupart de ces *patient-important outcomes* étaient des critères de mortalité alors qu'une très faible proportion était des critères de jugement rapportés par les patients évalués après le séjour en réanimation (qualité de vie, santé perçue et capacité fonctionnelle).

Dans un second travail, nous avons cherché à évaluer de quelle façon les décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives étaient rapportées dans les essais contrôlés randomisés en réanimation utilisant un critère de jugement de mortalité. Compte tenu de la fréquence importante de ces décisions chez les patients en situation critique et en considérant qu'elles pouvaient avoir une influence sur la survie des patients, nous avons fait l'hypothèse qu'elles devaient être rapportées en particulier lorsque l'étude était ouverte.

Les résultats de ce deuxième travail ont montré qu'un très faible nombre d'essais contrôlés randomisés en réanimation rapportaient ces décisions. Pour compléter ce travail, des simulations d'essais ont été réalisées montrant qu'un déséquilibre de ces décisions entre les 2 bras pouvait conduire à une interprétation erronée d'un critère de jugement de mortalité. Il est important de souligner qu'une prise de décision différentielle entre 2 groupes de randomisation peut refléter une préférence (ou conviction) de l'investigateur et donc un possible biais de performance, mais aussi un vrai effet lié purement à l'efficacité de l'intervention thérapeutique. En d'autres termes, des essais rapportant des délais différents de prises de décisions de limitation(s) thérapeutique(s) entre deux groupes ne sont pas systématiquement biaisés. Néanmoins une analyse de sensibilité prenant en compte ces prises de décisions (en les censurant par exemple) et montrant que les résultats ne sont pas quantitativement modifiés pourrait être un indicateur intéressant pour différencier ces deux situations.

Le troisième volet de notre travail fut de mener un essai contrôlé randomisé en réanimation en utilisant un *patient-important outcome* comme critère de jugement principal et en rapportant le taux et le délai des décisions de limitation(s) et d'arrêt(s) des thérapeutiques actives. Cet essai a permis de montrer qu'une stratégie d'attente d'épuration extra-rénale permettait à près de la moitié des patients de ne pas être exposés aux risques de cette technique sans différence de mortalité significative.

6/ PERSPECTIVES

6-1 Développement d'un groupe de critères de jugement incontournables (*Core outcome set*) en réanimation

Dans toutes les disciplines, l'objectif du développement de *core outcome sets* est de faciliter l'interprétation et la comparaison des travaux de recherche clinique (notamment dans les méta-analyses) (80). La première étape de ce développement est la réalisation d'une revue systématique afin d'identifier les critères de jugement et les outils de mesure des critères utilisés (81, 82). Alors qu'aucune taxonomie des critères de jugement en réanimation n'existe, notre travail sur les *patient-important outcomes* a permis de proposer une classification cohérente qui peut ainsi contribuer à cette première étape.

Dans l'objectif de faciliter le développement et l'application de *core outcome sets* en recherche clinique, le projet COMET (Core Outcome Measures in Effectiveness Trials) a vu le jour en 2010 (<http://www.comet-initiative.org>). Ces *core outcome sets* représentent les critères incontournables devant être rapportés dans un essai clinique. En aucun cas les investigateurs ne sont incités à n'utiliser que ces critères.

A ce jour, il n'existe qu'un projet en cours dans le domaine de la réanimation. Ce projet vise à développer un *core outcome set* dans le domaine de la ventilation mécanique (Core Outcomes in ventilation Trials (COVenT)) (83).

Ces *core outcomes sets* pourraient contribuer à la promotion des *patient-important outcomes* dans les essais randomisés en réanimation. Pour ce faire, certains auteurs ont proposé d'inclure les patients dans le processus de développement des *core outcomes sets* (84). Par ailleurs certains journaux comme le *British Medical Journal* incitent les chercheurs à impliquer les patients à tous les niveaux de la recherche et en particulier dans le choix des critères de jugement. Dans ce journal, les patients sont même impliqués dans le processus de *reviewing*.

Compte tenu de la spécificité des patients hospitalisés en réanimation et des conséquences à long

terme de leur séjour, cette démarche d'ouverture mérite d'être soutenue.

6-2 Développement d'outils de mesure de la qualité de vie après la réanimation

Une autre façon de promouvoir les *patient-important outcomes* dans les essais randomisés en réanimation est de fournir aux chercheurs des outils de mesure fiables et simples d'utilisation. Les outils de mesure de la qualité de vie utilisés dans les études en réanimation sont presque exclusivement des échelles génériques de qualité de vie (85): Sickness impact Profile (SIP), Short Form General Health Survey 36 (SF-36), RAND 36-items Health Survey (RAND-36), Nottingham Health Profile (NHP), EuroQol 5D (EQ-5D) (27). Ces échelles génériques présentent des limites pour leur utilisation chez les patients de post-réanimation. La longueur de ces questionnaires conduit parfois à un taux important de non-répondeurs conduisant à des difficultés d'interprétation (86). Bien que les échelles génériques aient été conçues pour comparer la qualité de vie de différentes populations, elles ne mesurent pas des dimensions spécifiques d'intérêt dans une situation donnée (87, 88). Dans de nombreux domaines (gastro-entérologie, maladies infectieuses, rhumatologie), des échelles spécifiques de qualité de vie (MOS-HIV, PROQOL-HIV, FDDQL), ont donc été développée (87–91).

Derek Angus (directeur du *CRISMA Center* qui fait autorité dans l'épidémiologie en réanimation) et Jean Carlet (ancien président du Comité Technique National des Infections Nosocomiales) ont publié les résultats d'une table ronde d'experts dont le sujet était « Vivre après les soins intensifs » (26). Les experts se posaient la question de l'existence du meilleur outil d'évaluation de la qualité de vie après la réanimation : « *Are existing instruments suitable for capturing important nuances of post-ICU sequelae or should disease-specific instruments be captured?* » Ils soulignaient que les échelles génériques existantes présentent des limitations, en particulier dans l'évaluation de l'impact séquelles neuro-cognitives. Ainsi, ils encourageaient les investigateurs à développer de nouveaux instruments

d'évaluation de la qualité de vie qui permettront de mieux prendre en compte la spécificité de ces patients dans l'évaluation thérapeutique ou pronostique.

Nous avons conçu une étude visant à développer une échelle de qualité de vie spécifique pour les patients sortis de réanimation à l'aide d'une méthodologie rigoureuse. Ce travail prévoit une implication importante des patients, de leurs proches, et d'experts multidisciplinaires impliqués dans la prise en charge de ces patients (médecins, kinésithérapeutes, infirmier(e)s, aides soignant(e)s, psychologues, assistantes sociales). La première étape consistera à générer des items sur la base d'une revue de la littérature (questionnaires existants), de l'avis des patients (et de leurs proches) et de l'avis d'experts (médecins, kinésithérapeutes, infirmier(e)s, aide-soignantes, psychologues, assistantes sociales). La méthode de consensus *Delphi* (92) permettra ensuite de recueillir les avis du groupe d'experts et de réduire le nombre d'items de manière consensuelle afin d'obtenir un questionnaire simple d'utilisation. L'échelle obtenue permettra de mettre à disposition des médecins et des chercheurs en réanimation un outil essentiel pour l'évaluation pronostique et thérapeutique en prenant mieux en compte la spécificité des patients sortis de réanimation. Ce projet que nous avons nommé ESQUALREA (Développement d'une Echelle Spécifique de QUALité de vie des patients après une hospitalisation en REAnimation) fera l'objet d'une demande de financement.

6-3 Promouvoir les recommandations sur le *reporting* des décisions de limitation des thérapeutiques actives

Nous avons fait 4 propositions de recommandations concernant le *reporting* des décisions de limitation(s) des thérapeutique(s) actives dans les essais randomisés en réanimation. Nous souhaitons les promouvoir en proposant une modification des recommandations CONSORT (CONsolidation Standard of Reporting Trials) (93) qui ont pour but d'améliorer le « *reporting* » dans la publication d'essais contrôlés randomisés. Nos résultats pourraient inciter les experts à

faire évoluer ces recommandations soulignant l'importance de rapporter le nombre de décisions de limitation(s) ou d'arrêt(s) des thérapeutiques actives dans les essais en réanimation qui utilisent la survie comme critère de jugement.

Dans l'avenir, une nouvelle revue systématique pourrait permettre d'évaluer l'application de ces nouvelles recommandations.

6-4 Protocole AKIKI 2

Le travail d'exploration des critères d'initiation de l'épuration extra-rénale en réanimation va se poursuivre. Dans l'essai AKIKI, l'épuration extra-rénale n'était indiquée dans le bras d'attente qu'en présence d'un des 5 critères suivants : hyperkaliémie menaçante, acidose métabolique ou mixte profonde, oedème pulmonaire de surcharge générant une hypoxémie importante, taux d'urée plasmatique > 40 mmol/l et durée de l'oligo-anurie > 3 jours. Les 2 derniers critères ne sont pas reconnus comme des critères d'initiation de l'épuration extra-rénale en urgence (94). Ils restent donc encore sujet de débat scientifique.

Notre projet est maintenant d'évaluer la pertinence de ne considérer comme critères d'initiation de l'épuration extra-rénale que les 2 derniers critères d'initiation dans le bras d'attente de l'essai AKIKI (l'urée plasmatique > 40 mmol/l et l'oligo-anurie de plus de 3 jours). Nous avons conçu la méthodologie de ce nouvel essai randomisé en incluant dans les critères de jugement secondaires un *patient-important outcome* qui n'est pas la mortalité : l'évaluation des activités quotidiennes des patients (Indice ADL de Barthel (95)). Par ailleurs, de la même façon que dans notre premier travail, les décisions de limitation(s) et d'arrêt(s) des thérapeutiques actives feront partie des critères de jugement secondaires de l'essai et seront rapportées selon les recommandations que nous avons émises dans l'article : *Withdrawal of life support therapies reporting in randomized controlled trial in critically ill patients: a systematic review and a statistical simulation study*.

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